CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201200257

Total Synthesis of Branimycin: An Evolutionary Approach

Valentin S. Enev, Wolfgang Felzmann, Alexey Gromov, Stefan Marchart, and Johann Mulzer*[a]

Abstract: The first total synthesis of the macrolactone antibiotic branimycin (4) has been described. The key disconnection leads to a *cis*-dehydrodecalone core and a polyketide side chain which are connected via organometallic addition. The dehydrodecalone core was targeted via altogether five different approaches featuring various kinds of chiral elements and ring-closing methodology. In the end the most successful method starting from diepoxynaphthalene **109** was chosen to carry on with the synthesis. Thus the oxygen functions and carbon appendages were introduced via organometallic desymmetrization reactions to generate epoxy ketone **107**, to which vinyl iodide **11** was added after conversion into the organolithium species. The synthesis was completed by introducing the ester side chain via Michael addition and subsequent macrolactonization.

Keywords: antibiotics · Diels–Alder reaction · macrolactone · natural products · polyketide · ring-closing metathesis

Introduction

The nargenicin family of antibiotics as represented by compounds **1**, **2** and **3** (Figure 1), which have been isolated from the fermentation of *Nocardia argentinensis* nov. gen. (ATCC 31306) and the soil organism *Saccharopolyspora hirsuta*[1–5a] show distinct antibacterial activity, the most against *Staphylococcus aureus*, including strains that are resistant to other antibiotics. They are further active against *Bacillus subtilis*, *Streptococcus pyogenes*, *Pasteurella multocida* and *Neisseria sicca* (Nargenicin A_1) and *Staphylococcus epidermidis* (CP 51467). Quite recently, the antibacterial activity of **1** was reevaluated and it turned out to be superior to that of a variety of classical antibiotics.[5b]

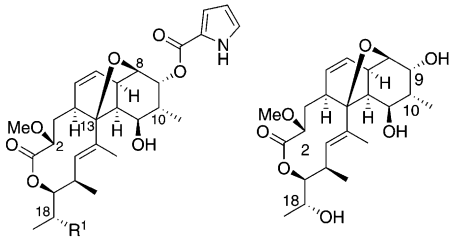


Figure 1. Some nargenicin antibiotics.

In 1998 the Laatsch group screened the culture broth of the *Streptomyces* stem GW 60/1571,[6] and found that it was active against *E. coli*, *Bacillus subtilis*, *Streptomyces viridochromogenes* and *Staphylococcus aureus*. Fractioning and purification showed this activity to be derived from a substance, where the NMR signals did not match the structures published in the databases. The basic C–C connectivities could be determined by extensive NMR analysis—full structural assignment was possible by comparison with the NMR data available for nargenicin A_1 (**1**) followed by adaption of the stereochemistry based on NOE interactions. The substance was called branimycin (**4**, Figure 2).

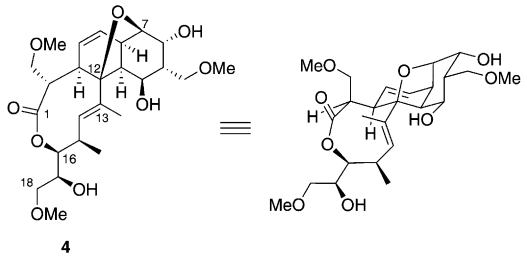


Figure 2. Postulated structure of branimycin (**4**).

The structure of branimycin (**4**) is characterized by a densely functionalized *cis*-dehydrodecalin core, with the familiar transannular oxo-bridge. Annulated to the dehydrodecalin is a nine–membered macrolactone ring, containing a trisubstituted (*E*)-double bond. The stereocenters on the C-13–C-18 polyketide chain of the macrolactone are in a *syn*,*syn* relationship. In comparison with nodusmycin, C-2 is shifted to an exocyclic position in branimycin, resulting in a one-carbon contracted nine-membered macrolactone ring. Additionally, the 10- and 19-methyl groups are oxygenated

[a] Dr. V. S. Enev, Dr. W. Felzmann, Dr. A. Gromov, Dr. S. Marchart, Prof. J. Mulzer
University of Vienna, Institute of Organic Chemistry
Währinger Strasse 38, 1090 Vienna (Austria)
Fax: (+43) 1-4277-52189
E-mail: johann.mulzer@univie.ac.at

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200257.

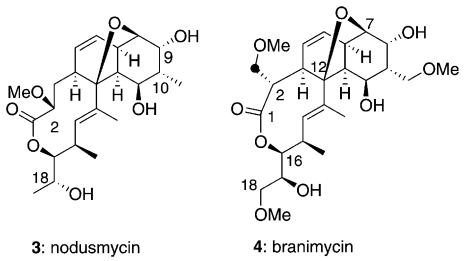


Figure 3. Comparison of nodusmycin and branimycin.

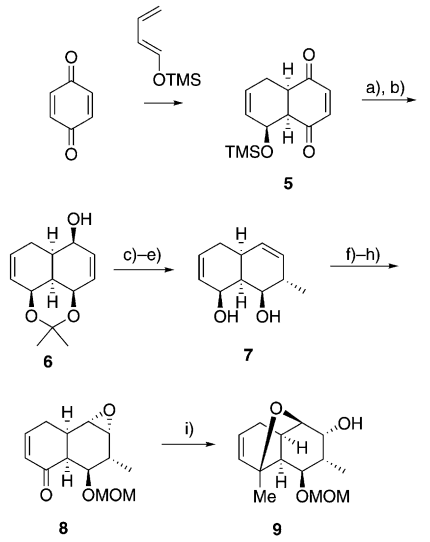
and the relative configuration at C-18 is inverted (now C-17 in **4**, Figure 3).

Our motivation to launch a total synthesis of branimycin[7] fivefold: 1) It is the most complex member in the family. 2) The antibiotic properties are promising. 3) Total synthesis is the only way to check the structure assigned so far on the basis of spectroscopic analyses only. 4) There is just one completed total synthesis of a nargenicin antibiotic (18-desoxynargenicin A_1 by Kallmerten[8]), despite serious attempts from other groups.[9] Obviously, the complex structure of **4** is, even in the light of modern synthetic methodology, a worthwhile challenge. 5) A total synthesis would provide access to suitable derivatives for later structure–activity relationship (SAR) studies.

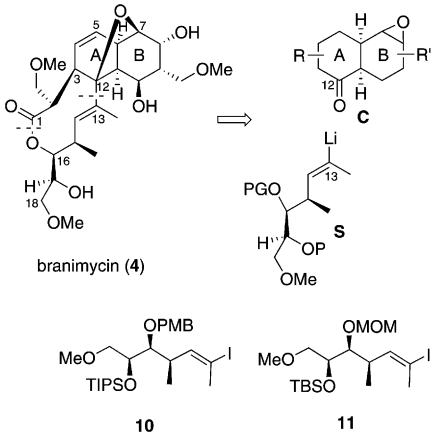
Retrosynthetic considerations: Our retrosynthetic plan was strongly inspired by the synthetic efforts towards the total synthesis of nargenicin A_1 which were reported in 1984 by the Kallmerten group.[10] These authors disconnected the molecule into two parts, the *cis*-dehydrodecalin unit and the polyketide side chain. The dehydrodecalin skeleton was synthesized in racemic form by intermolecular Diels–Alder reaction of 1-(trimethylsilyloxy)butadiene and *p*-benzoquinone to yield the *endo*-adduct **5** (Scheme 1). DIBAL-H reduction and subsequent protection of the 1,3-diol gave acetonide **6**, which could be converted to **7** by an S_N2' displacement with a methylcuprate followed by acidic hydrolysis. The allylic alcohol could be oxidized selectively, and the remaining free hydroxyl group was protected as a MOM ether. Epoxidation of the non-conjugated double bond with *m*CPBA led to epoxide **8**. When treated with methylmagnesium bromide as a test reaction, **8** furnished first a tertiary alcohol from the ketone, which then opened the epoxide to yield the oxo-bridged bicycle **9**. This strategy was successfully extended to 18-desoxynargenicin (**2**) later on.[8]

Following this general concept our retrosynthesis aims at the disconnection of branimycin (Scheme 2) into the metalated side chain **S** (in form of vinyl iodides **10**/**11**, which have been described earlier[7e]) and the decalin core **C**.

This report will be focused on the synthesis of **C**. Our general strategy was designed so as to develop as many competing approaches as possible and to push forward with the most promising one to the end. The reader may want to go directly to Scheme 28, and will find, in the ensuing paragraphs, the finally successful route to **4**.



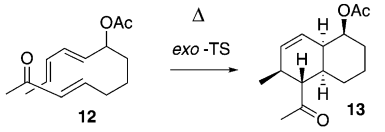
Scheme 1. Kallmerten's approach to racemic dehydrodecalin **9**. a) DIBAl-H; b) 2,2-DMP, H^+; c) MsCl; d) MeCu, $BF_3{\cdot}OEt_2$; e) 1 N HCl; f) PDC; g) MOM-Cl, *i*$PrNEt_2$, h) *m*CPBA; i) MeMgBr. MOM = methoxymethyl.



Scheme 2. General retrosynthetic analysis of branimycin (**4**).

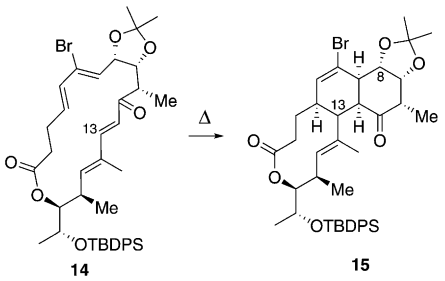
Results and Discussion

Intramolecular Diels–Alder (IMDA) reaction: In contrast to the intermolecular Diels–Alder reaction used by Kallmerten, Jones et al.[11] decided to construct the *cis*-dehydrodecalin ring in nargenicin via a biomimetic intramolecular Diels–Alder (IMDA) approach. In a model study, trienone **12** underwent an *exo*-selective cycloaddition to give *cis*-dehydrodecalin **13** (Scheme 3).



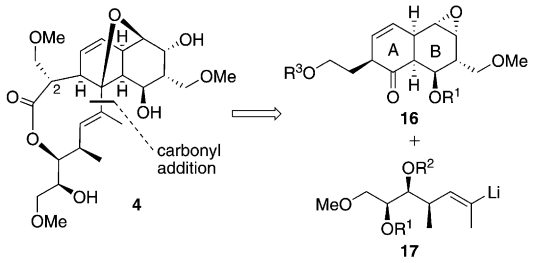
Scheme 3. IMDA reaction by Jones.[11]

In a related approach to nargenicin, Roush et al. studied IMDA[12] and later also TADA (transannular Diels–Alder reaction)[13] variations. They demonstrated that macrolactone **14** underwent thermal TADA cyclization selectively to *cis*-dehydrodecalin **15** (Scheme 4), however, the requisite oxo-bridge could not be introduced after the TADA reaction by allylic oxidation or remote functionalization and C-10 epimerized under the conditions.



Scheme 4. Roush's TADA reaction of the 18-membered macrolactone **14**.

Thus, in keeping with our retrosynthetic strategy (cf. Scheme 2) and contrary to Roush's approach, we restricted the TADA[14] approach to access the dehydrodecalone core **16** only and planned to add the side chain **17** (generated from lithiation of **10**/**11**) later (Scheme 5).[7a]

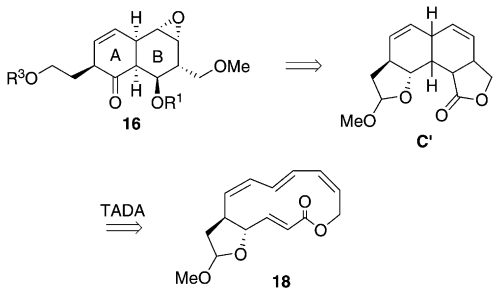


Scheme 5. Planned disconnection of branimycin (**4**) into *cis*-dehydrodecalone (**16**) and side-chain **17**.

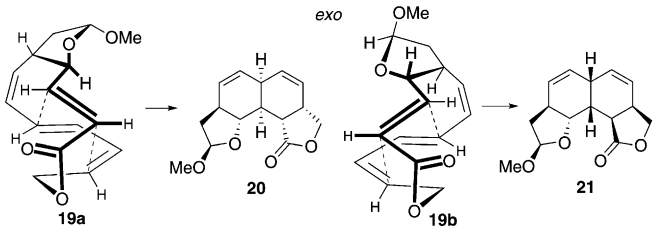
To keep the TADA as simple as possible, **16** was modified to reveal precursor **C′** which could be formed from macrolactone **18** via TADA (Scheme 6). The lactol ring in **18** should serve as a chiral template to induce suitable conformations for the transannular cycloaddition. Provided **C′** can be obtained with the correct relative configurations the desired compound **16** might be in reach.

To get more information on the possible stereochemical course of this TADA reaction high-level DFT calculations[15] were performed (for details see Supporting Information) which showed that *endo*-transitions states are much too strained, whereas the *exo* transition states **19a** and **b** (Scheme 7) would be viable, with a significant preference for **19a**. So the desired product **20** should be available.

On this basis we initiated the synthesis of macrolactone **18**. The polyene moiety should be installed by a combination of olefination and cross-coupling methodology.

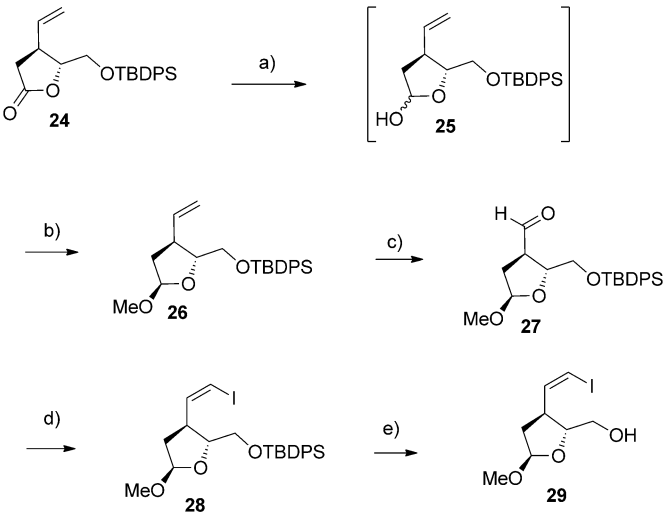


Scheme 6. Envisaged TADA approach to the branimycin core **16** via **C′**.

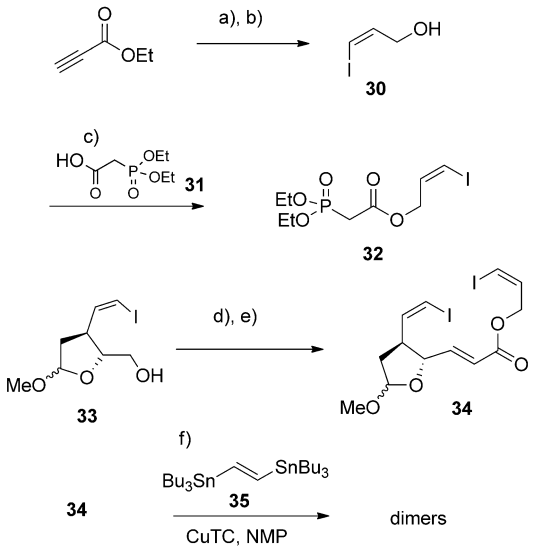


Scheme 7. TADA transition states as calculated by DFT.

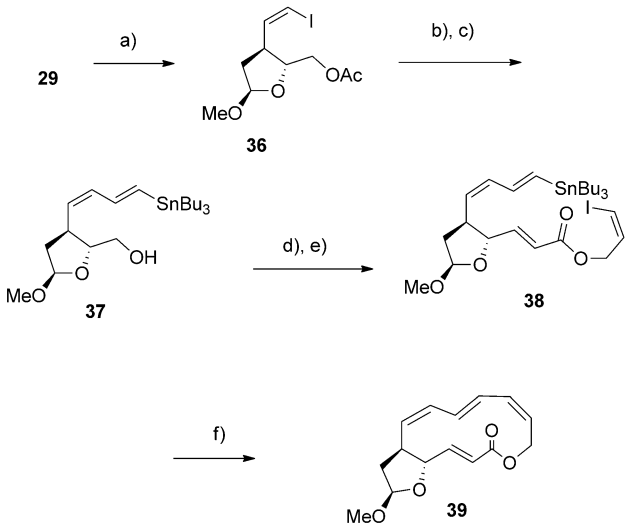
Known lactone **24**[7c] was reduced to give lactol **25** as an anomeric mixture (Scheme 8). Whereas treatment with methanol and acid led to anomeric mixtures (**33**, Scheme 9), methylation under equilibrating basic conditions resulted in dynamic kinetic resolution to furnish pure methyl acetal **26**. Ozonolysis and Wittig–Stork–Zhao olefination[16a] led to vinyl iodide **28** which was deprotected to give alcohol **29**. In a parallel set of reactions phosphonate **32** was prepared from ethyl propiolate via (*Z*)-iodo-allylic alcohol **30** (Scheme 9).[16b] The aldehyde obtained from in situ oxidation of **33** was subjected to a Roush–Masamune olefina-



Scheme 8. Synthesis of vinyl iodide **29**. a) DIBAL-H (1.5 M in toluene), Et_2O, −78 °C, 1 h; b) Ag_2O, MeI, CH_2Cl_2, reflux, 48 h, 85 % from **24**; c) O_3, CH_2Cl_2, −78 °C, then PPh_3, 0 °C, 14 h, 83 %; d) $PPh_3PCH_2I^+I^-$, THF, NaHMDS, 1 min, RT, then HMPA, **27**, −78 °C, 30 min, 83 %; e) NH_4F, MeOH, RT, 14 h, 82 %. DIBAL-H = diisobutylaluminum hydride.



Scheme 9. Failed Stille macrocyclization. a) Acetonitrile, LiI, AcOH, reflux; b) DIBAL-H (1.5 M in toluene), Et_2O, 0 °C, 30 min, 87 % over two steps; c) CH_2Cl_2, **31**, oxalyl chloride, 0 °C, 20 min, then **30**, pyridine, DMAP, RT, 14 h, 87 %; d) acetonitrile, IBX, reflux, 30 min; e) aldehyde added to **32**, LiCl, DBU in acetonitrile, RT, 3 h, 60 %; f) THF, **35**, [Pd-$(PPh_3)_4$], CuTC, NMP 40 °C. DBU = 1,8-diazabicycloundec-7-ene, DMAP = 4-dimethylaminopyridine; IBX = 2-iodoxybenzoic acid; NMP = *N*-methyl-2-pyrrolidinone; CuTC = copper(I)thiophene-2-carboxylate.

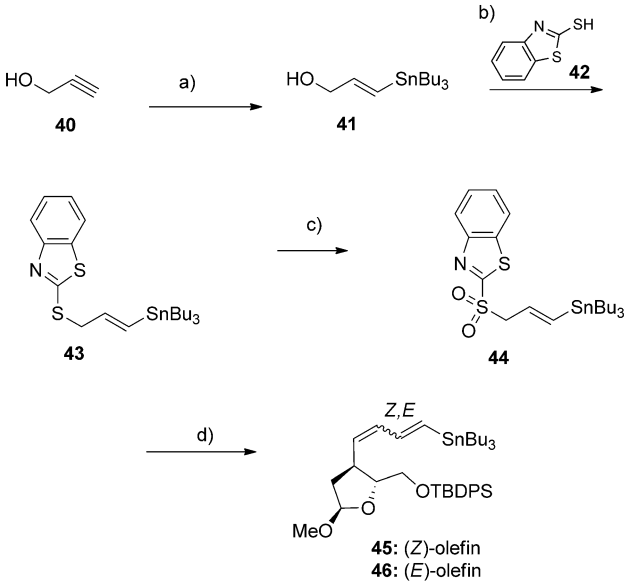


Scheme 10. sp^2–sp^2 Stille coupling to give **39**. a) AcCl, pyridine, RT, 14 h, 83 %; b) toluene, [$Pd(PPh_3)_4$], **35**, RT, 14 h; c) DIBAL-H (1.5 M in toluene), Et_2O, 0 °C, 30 min, 93 % over two steps; d) 4 Å MS, CH_2Cl_2, NMO, TPAP, RT, 30 min; e) aldehyde added to acetonitrile, LiCl, **32**, DBU, RT, 1 h, 75 %; f) DMF, [Pd_2dba_3], $CHCl_3$, P(*O*-furyl)$_3$, CuI, RT, 36 h, 51 %. TPAP = tetra-*n*-propylammonium perrhutenate.

tion[17] with **32**. Diiodo enoate **34** was obtained and subjected to Stille "stitching" cross-coupling with distannane **35**.[18] However, under a variety of conditions highly labile dimers were formed (Scheme 9). It was noted that under all conditions, the (*Z*)-iodo-allylic ester was consumed in the reaction, whereas the (*Z*)-iodo olefin on the methyl lactol remained untouched. Therefore, an alternative coupling was attempted (Scheme 10). Alcohol **29** was acetylated to give **36**, and then cross-coupled with **35** to furnish *seco*-intermediate **38** which underwent Stille cyclization to form the desired macrolactone **39** in moderate yield. A variety of similar Stille couplings were performed though with no success (see Supporting Information).

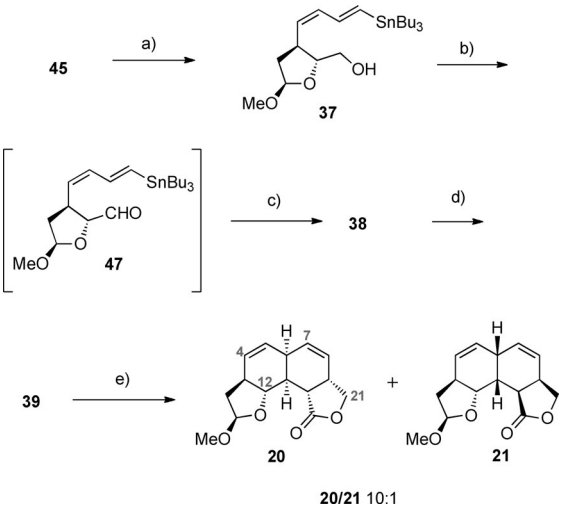
Due to the unfavorably large amounts of (*E*)-1,2-bis-(tributylstannyl)-ethene (**35**) required in the synthesis of the (*Z*,*E*)-dienylstannane **37**, we looked for alternatives. Much to our avail, Brückner and Sorg[19] reported that the (Sylvestre) Julia olefination of vinyltin bearing sulfone **44** with a variety of aldehydes gave much higher *Z* selectivity than that usually observed with such sulfones.[20] The preparation of **44** was accomplished in a three-step sequence from 2-propyn-1-ol (**40**), as shown in Scheme 11. Subjection of this sulfone to the olefination conditions reported[19] led to a *Z*/*E* mixture of 9:1, delivering the desired (*Z*,*E*)-dienylstannane **45** in 61 % yield.

The TBDPS group in **45** was removed and the resulting alcohol was oxidized to aldehyde **47** which underwent smooth olefination with phosphonate **33** to give *seco*-compound **38**. Modified Stille coupling, using tetrabutylammonium diphenylphosphinate[21] as a tin scavenger, led to macrolactone **39** in 65 % yield (Scheme 12).



Scheme 11. (*Z*)-Selective Julia olefination. a) Bu_3SnH, AIBN, toluene, 80 °C, 2 h, 60 %; b) DIAD, PPh_3, **42**, THF, 0 °C → RT, 14 h, 89 %; c) $(NH_4)_6Mo_7O_{24}{\cdot}7H_2O$, 30 % H_2O_2, EtOH, 0 °C, 24 h, 99 %; d) toluene, **44** + **27**, KHMDS (0.5 M in toluene), −78 °C, 8 h, then RT, 14 h, 61 %. AIBN = azobisisobutyronitrile; DIAD = diisopropyl azodicarboxylate; KHMDS = potassium hexamethyldisilazide.

For the TADA reaction, **39** was refluxed in xylenes for 36 h. To avoid oxidation of the double bonds at these elevated temperatures, 2,6-bis-*tert*-butyl-4-methyl phenol (BHT) was added to the reaction mixture. Under these conditions, the TADA product **20** was obtained in 80 % yield.



Scheme 12. TADA to form branimycin core **20**. a) TBAF, THF, RT, 2 h, 85 %; b) 4 Å MS, CH_2Cl_2, NMO, TPAP (5 mol %), 30 min; c) **32**, acetonitrile, LiCl, DBU, RT, 5 min, then add to **47**, 1 h, 75 %; d) THF, **38**, [Pd(PPh_3)$_4$], LiCl, $Bu_4NPh_2PO_2$, 40 °C, 18 h, 65 %; h) xylenes, BHT (30 mol %), reflux, 36 h, 80 %. BHT = 2,6-bis-*tert*-butyl-4-methylphenol.

The relative configuration of **20** was assigned by extensive analysis of the NOESY spectra. Key NOE interactions are shown in Figure 4a, most important are the clear interactions between H-12 and H-9, as well as H-3 and H-11. Slow recrystallization from hexanes/chloroform yielded crystals suitable for X-ray single crystal diffraction (Figure 4b). This crystal structure[7b] not only confirms the proposed stereochemistry, it also explains the observed NOE interactions, especially between C-9 and C-12. Finally, the crystal structure is in perfect accordance with the structure proposed by molecular modelling. Additionally the DFT analysis of the transition states was confirmed.

Further experiments, carried out with larger amounts of **39**, allowed the characterization and identification of the second *exo*-TADA product **21**, formed in a ratio of **20**/**21** 10:1. Again, the configuration of **21** was assigned from the NOESY spectra. This is clear evidence that the TADA reaction is highly *exo*-selective, with a significant preference for **20**.

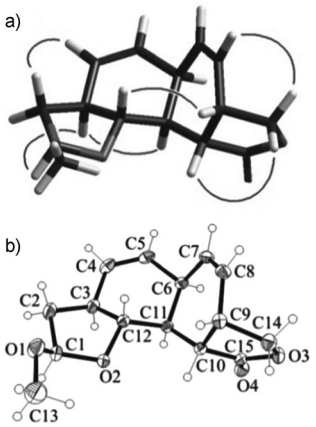
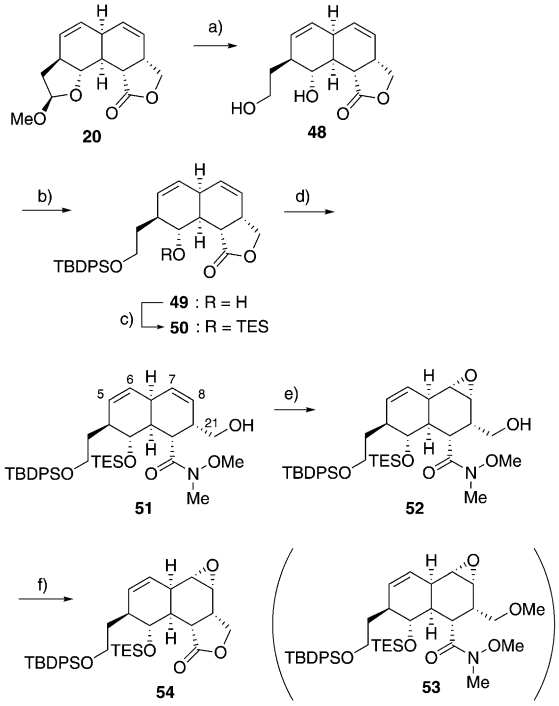


Figure 4. a) Observed NOE interactions on 3D model of **20**. b) ORTEP projection of the crystal structure of the TADA product **20**.

To move on into the direction of the desired intermediate **16**, acetal hydrolysis with aqueous HCl and subsequent reduction of the free lactol with $NaBH_4$ gave the diol **48** in quantitative yield (Scheme 13). Sequential silylation of the



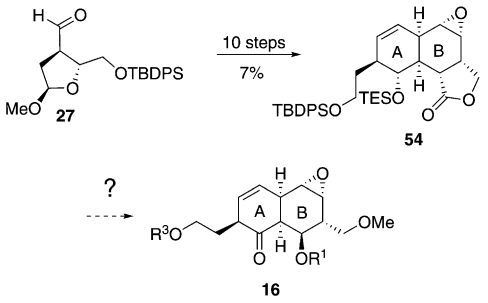
Scheme 13. Further processing of **20**. a) THF, aq. HCl (0.5 M), 40 °C, 1 h, then add $NaHCO_3$ and $NaBH_4$, RT, 10 min, quant.; b) TBDPSCl, DMF, DMAP, Et_3N, RT, 14 h, 60 %; c) TESOTf, CH_2Cl_2, Et_3N, 0 °C → RT, 4 h, 90 %; d) MeNHOMe·HCl, *i*PrMgCl, THF, 0 °C → RT, 1 h, 85 %; e) *m*CPBA, CH_2Cl_2, phosphate buffer pH 7, RT, 40 min, 65 %; f) THF, NaH, MeI, 0 °C → RT, 2 h, 65 %. TBDPS = *tert*-butyldiphenylsilyl, TES = triethylsilyl.

two OH functions led to **49**/**50**. Next the lactone was opened to form Weinreb amide **51**. Directed epoxidation furnished **52** regio- and stereoselectively. Methyl ether **53** was generated in small amounts, however, the main reaction resulted in the formation of lactone **54**, whose structure was assigned by NOESY spectroscopy.

In conclusion, the synthesis of chiral dehydrodecalin **54** from aldehyde **27** proceeded in 10 steps and 7 % overall yield (Scheme 14). Although **54** seems close to the targeted structure **16**, we decided to abandon this route, due to more promising developments in our group.

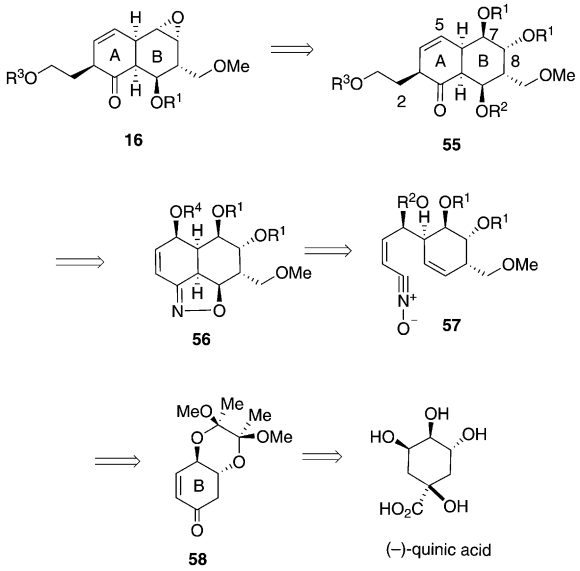
Quinic acid routes to 16

Intramolecular nitrile oxide cycloaddition (INOC) annulation: In search of a suitable inexpensive chiral starting material we opted for cyclohexenone **58** (easily available from



Scheme 14. Summary of the TADA approach.

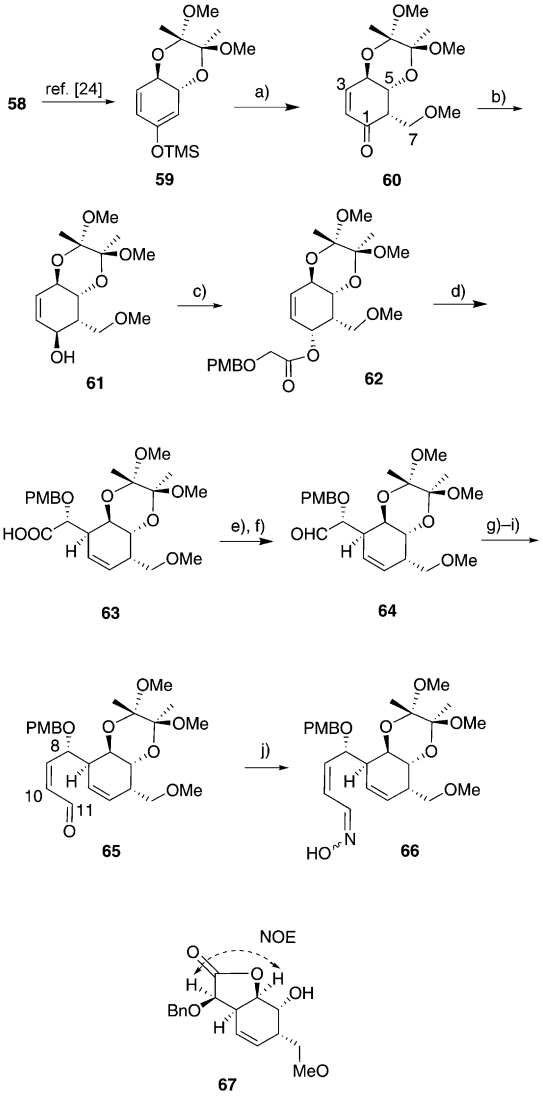
(−)-quinic acid) which contains already ring B in modified form (Scheme 15). For annulating ring A we chose an intramolecular nitrile oxide olefin cycloaddition (INOC)[22] of intermediate **57**. Based on literature precedence[22] we expected that isoxazoline **56** be formed stereoselectively which could then be reduced to a hydroxyl ketone and by means of a Claisen-type rearrangement[23] compound **55** should be accessible.



Scheme 15. Retrosynthetic considerations of **16** starting from quinic acid.

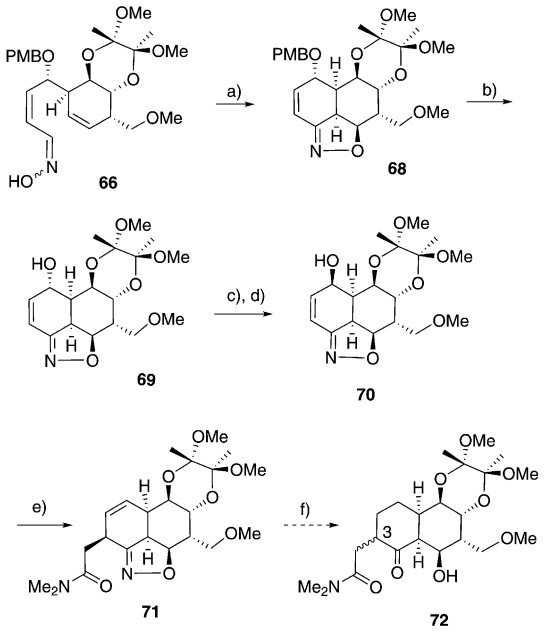
We started with the conversion of ketone **58** into the silylenol ether **59** (Scheme 16).[24] After intensive investigation we found that compound **59** reacts with dimethoxymethane in the presence of 5 mol% TMSOTf[25] to give **60**[26] as a single diastereomer in 55% yield (73% after recycling of the starting material).

After reduction to alcohol **61** a Mitsunobu esterification[39] with $PMBOCH_2COOH$ led to the protected glycolate ester **62** which on chelation-controlled Burke–Kallmerten–Claisen rearrangement[27] furnished acid **63** as a single isomer whose configuration was confirmed by transformation to lactone **67** and NOE experiments. Formation of the methyl ester was followed by DIBAL-H reduction to afford aldehyde **64**.



Scheme 16. Synthesis of oxime **66**. a) $CH_2(OMe)_2$, TMSOTf, 2,6-di-*tert*-butylpyridine, 55%; b) $NaBH_4/CeCl_3$, quant.; c) PPh_3, DEAD, $PMBOCH_2COOH$, THF/CH_2Cl_2, 0°C, 24 h, 93%; d) LiHMDS/TMSCl, THF −78 → 0°C, 91%; e) $TMSCHN_2$, toluene/MeOH; f) DIBAL-H, CH_2Cl_2, −78°C, 3.5 h, 80%; g) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, KHMDS, [18]crown-6, THF, −78°C, 88%; h) DIBAL-H; i) DMP/$NaHCO_3$, 86%; j) $NH_2OH{\cdot}HCl$, 2,6-di-*tert*-butylpyridine, 4 Å MS, 60%. DMP = Dess–Martin periodinane; PMB = *para*-methoxybenzyl; DEAD = diethyl azadicarboxylate.

Still–Gennari olefination,[28] reduction of the ester to the alcohol and reoxidation delivered (*Z*)-aldehyde **65** in 76% yield. For the conversion of **65** to oxime **66** the use of nonnucleophilic 2,6-di-*tert*-butylpyridine as a base was essential to avoid *E*/*Z* isomerization of the olefinic double bond. The INOC reaction (Scheme 17) was initiated by heating oxime **66** with 1.1 equiv of NCS and a catalytic amount of pyridine. The resulting nitrile oxide immediately cyclized to isoxazoline **68** in 92% yield, for which the configuration was secured by NOE experiments. The PMB group was removed and the resulting alcohol **69** was inverted to **70** and then subjected to an Eschenmoser–Claisen rearrangement[23,59]

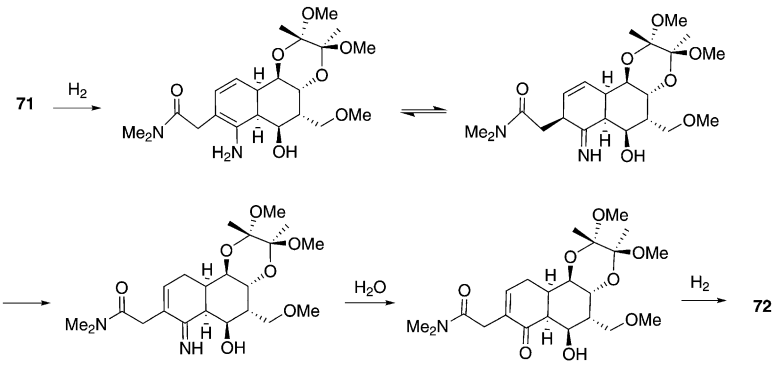


Scheme 17. INOC approach to **71**. a) NCS, pyridine, $CHCl_3$, 60 °C, 92 %; b) DDQ, CH_2Cl_2, 77 %; c) DMP, 89 %; d) $NaBH_4$, $CeCl_3$, 96 %; e) $Me_2NCH(OMe)_2$, 4 Å MS, xylene, 155 °C, 82 %; f) H_2, Raney Ni, H_3BO_3, 81 %. DDQ = 2,3-dichloro-5,6-dicyano-*p*-benzoquinone; NCS = *N*-chlorosuccinimide.

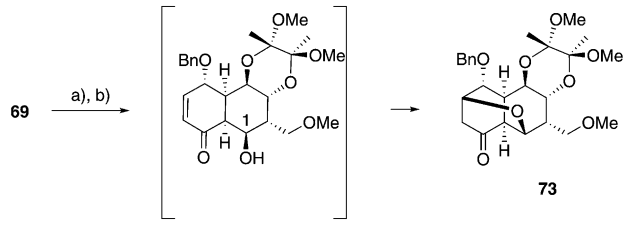
which furnished amide **71** in high yield. Unfortunately, the reductive opening of the isoxazoline with hydrogen in the presence of Raney-Ni and boric acid[29] led to hydrogenation of the double bond and epimerization at C-3 to give **72**.

This surprising yet highly undesirable result was interpreted in terms of an imine–enamine tautomerization[30] followed by reduction (Scheme 18).

All attempts to suppress the formation of the enamine by other reduction conditions (H_2 + Pd/C,[31] Rh/$CaCO_3$, Lindlar catalyst,[32] SmI_2[33]) and/or Lewis and Brønsted acids ($AlCl_3$, $BF_3{\cdot}Et_2O$, 1 N HCl), were not successful. Thus, we changed the order of the steps and decided to reduce the isoxazolidine with $[Mo(CO)_6]$[34] prior to the Claisen rearrangement. Unfortunately this led to the cyclic ether **73** via a transannular 6-*endo*-*trig*-oxa-Michael cyclization of the intermediate 1-hydroxy-enone (Scheme 19).



Scheme 18. Postulated formation of **72**.

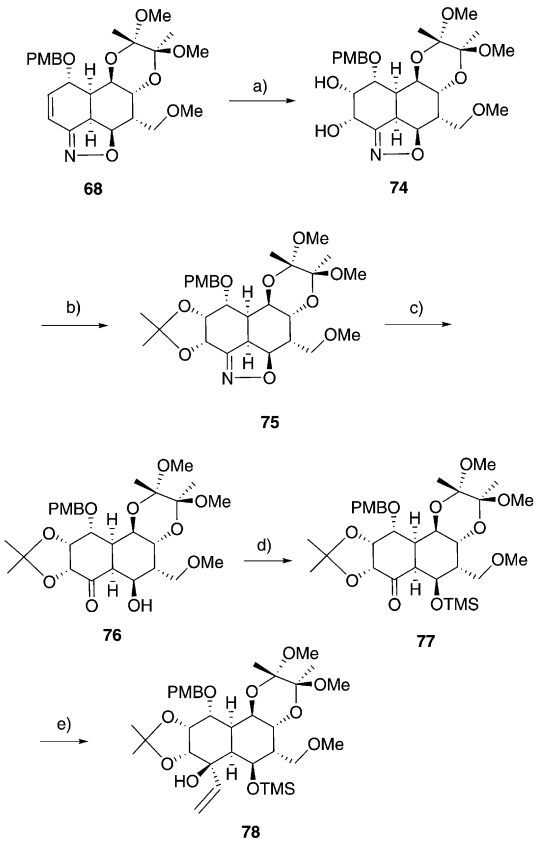


Scheme 19. Formation of transannular ether **73**. a) BnBr, NaH, THF, RT, 86 %; b) $[Mo(CO)_6]$, $MeCN/H_2O$, reflux, 82 %.

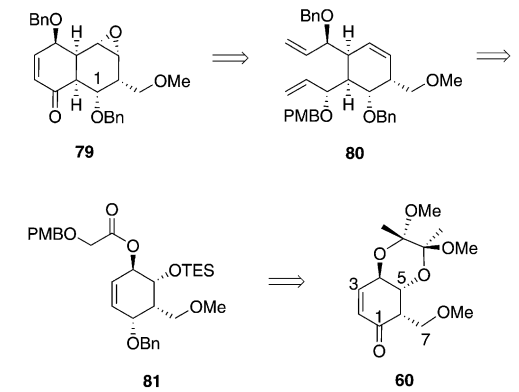
To avoid the formation of **73**, the double bond in **68** was oxidized to diol[35] **74** stereoselectively (Scheme 20) and protected as acetonide **75**. Now, the cleavage of the isoxazoline proceeded smoothly to give β-hydroxy ketone **76** in 92 % yield. After protection as TMS ether **77** the addition of vinylmagnesium bromide furnished alcohol **78** (72 %) with high stereoselectivity. Despite this favorable outcome this approach needed too many protecting operations and was abandoned.

RCM annulation: Obviously, the INOC route was problematic for producing intermediate **55**. Thus, an alternative route was chosen in which ring B in intermediate **79** should be constructed by a ring-closing metathesis[36] (RCM) of triolefin **80**, so that the interfering 1-OH group could be protected beforehand and the transannular Michael addition is prohibited (Scheme 21).

The two exocyclic olefins were to be installed via two successive Claisen–Ireland rearrangements from the protected triol precursor **81**, which would be gained from enone **60**. Our synthesis (Scheme 22) started with the stereoselective formation of **82** from enone **60**. Regioselective esterification of 7-OH with protected glycolic acid to **81** was followed by Ireland–Claisen rearrangement and esterification of the acid to furnish methyl ester **83**. The low stereoselectivity at C-12, presumably due to lack of *E*/*Z* control of the silylketene acetal intermediate (internal quench[37]), was inconsequential as this stereogenic center is to be oxidized later in the synthesis. Nevertheless, the diastereomers were separated to simplify the NMR spectra for the following intermediates. The pure main isomer β-**83**, whose configuration was assigned by 2D NMR studies of the corresponding iodolactone,[38] was transformed to the corresponding olefin in three steps. The second Claisen–Ireland rearrangement required a Mitsunobu inversion[39] to form ester **84**, whose transformation to di-olefin **80** followed the established four-step protocol (d.r. 2:1, 56 % overall yield[40]). The RCM reaction was performed with the Grubbs′ 2nd generation catalyst[41] and the Hoveyda–Grubbs′ 2nd generation cata-

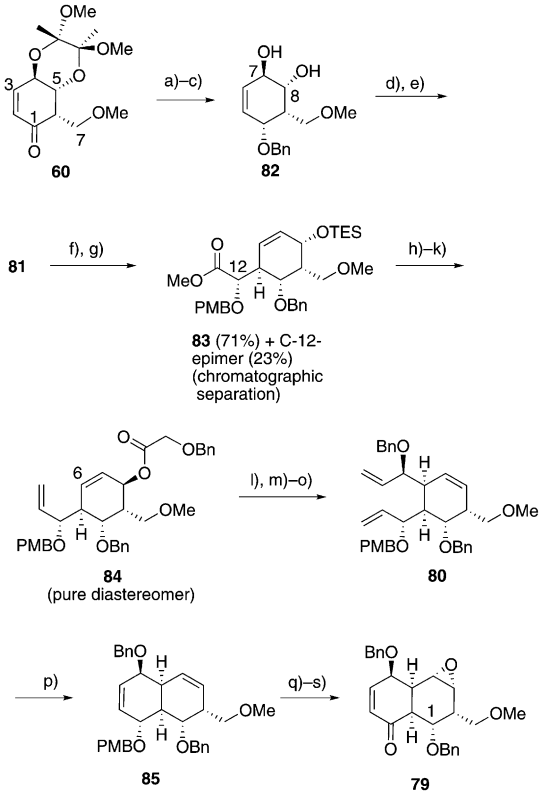


Scheme 20. Reductive opening of isoxazoline **75**. a) 2 equiv OsO_4, pyridine, −25 °C, 86 %; b) $Me_2C(OMe)_2$, PTS, 48 h, 97 %; c) H_2, Raney-Ni, H_3BO_3, 30 min, 90 %; d) TMSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 56 %; e) vinylmagnesium bromide, THF, −78 °C, 72 %. PTS = *p*-toluene sulfonic acid.



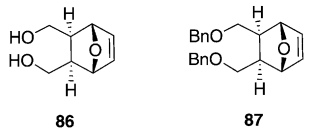
Scheme 21. Revised retrosynthetic analysis.

lyst.[42] Whereas the Grubbs′ 2nd generation catalyst did not survive at the required reaction temperature (ca. 75 °C), the Grubbs–Hoveyda catalyst was stable enough to give 65 % of the *cis*-decalin (2:1 mixture of diastereomers) along with 30 % starting material (Scheme 22). After chromatographic separation the pure isomer **85** was converted to the ketone. Stereo- and regioselective epoxidation of the C-7−C-8 double bond with *m*CPBA furnished diastereomerically pure crystalline epoxy ketone **79** whose relative configuration was established by single crystal diffraction.[7d] At this stage we had shown that quinic acid is a suitable substrate for stereocontrolled annulations via the Claisen–Ireland rearrangement–RCM protocol. As diol **82** can be acylated under retention or inversion of configuration, *cis*- and *trans*-fused decalins should be available under predictable and perfect sterecontrol. However, in the present case, the overall transformation of **60** into **79** required no less than 15 steps and the configuration at C-1 has to be inverted yet at some later stage.



Scheme 22. Synthesis of dehydrodecalone **79**. a) $CeCl_3$, $NaBH_4$, MeOH, 0 °C, 15 min; b) NaH, BnBr, Bu_4NI, THF/DMF, RT, 18 h; c) TFA/H_2O, RT, 5 min, 80 %, for three steps; d) 2,6-DTBP, *p*-$MeOC_6H_4OCH_2COCl$, toluene, −18 → 22 °C; e) TESOTf, 2,6-lutidine, CH_2Cl_2, −78 °C, 82 % for two steps; f) TMSCl, LHMDS, THF, −78 → 65 °C; g) $TMSCHN_2$, toluene/MeOH, RT, 94 % for two steps. After separation of the isomers the sequence was carried on with the pure main isomer: h) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; i) Ph_3PCH_3Br, KO*t*Bu, THF, RT, 10 min; j) NH_4F, MeOH, RT, 3 h; k) PPh_3, DEAD, $BnOCH_2COOH$, THF/CH_2Cl_2, 0 °C, 24 h, 63 % for four steps starting with **83**); l) TMSCl, LHMDS, THF, −78→65 °C; m) $TMSCHN_2$, toluene/MeOH, RT; n) DIBAL-H, CH_2Cl_2, −78 °C, 3 h; o) Ph_3PCH_3Br, KO*t*Bu, THF, RT, 10 min, 56 % for five steps; p) Hoveyda–Grubbs′ II cat, toluene, 75 °C, 16 h, 65 %; q) DDQ, CH_2Cl_2/buffer (pH 7), RT, 1.5 h; r) DMP, $NaHCO_3$, CH_2Cl_2, RT, 20 min, 78 % for two steps; s) *m*-CPBA, $CHCl_3/H_2O$, pH 7, RT, 6 h, 82 %. DTBP = 2,6-di-*tert*-butylpyridine.

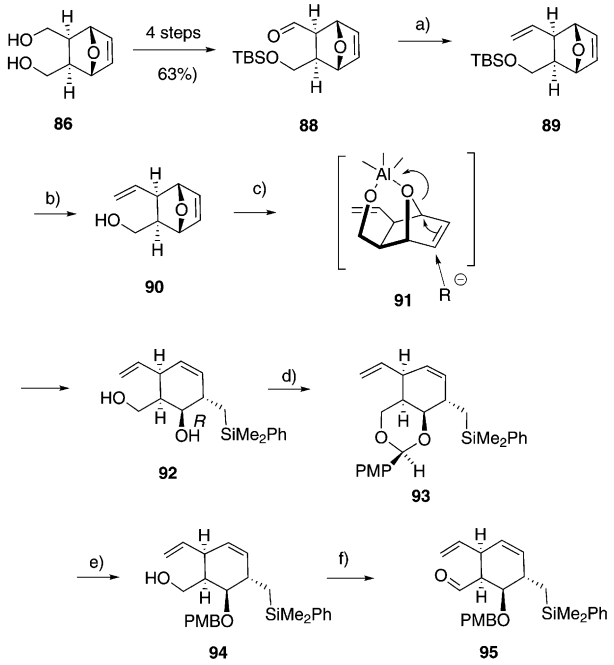
Desymmetrization approaches: Trusting on the applicability of the RCM we looked for a more direct route to a suitable diene substrate. Obviously, the desymmetrization[43–45] of the known oxabicyclic compound **86** or **87**[46] (Scheme 23) fol-



Scheme 23. Substrates for desymmetrization.

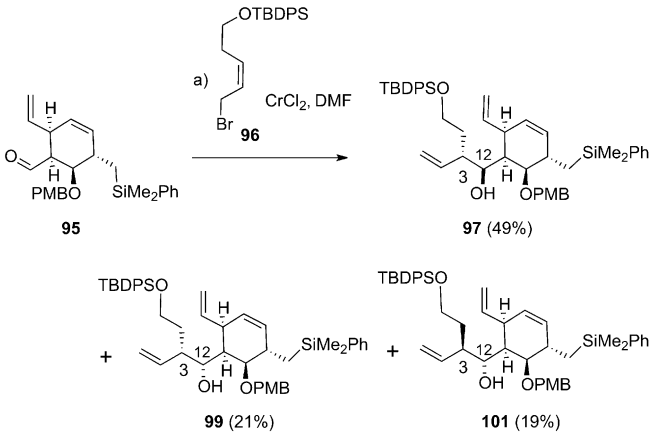
lowed by converting the two hydroxy-methylene side chains into suitable olefins should provide a straightforward access to a *cis*-decalin system.

The synthesis started with the known four-step conversion of **86** into aldehyde **88**[46] via enzymatic enantiotopos selective acetylation (Scheme 24).[47] Wittig olefination of **88** to form **89** was followed by desilylation to alcohol **90**, whose S_N2' reaction with $PhMe_2SiMgCl/CuCl/EtAlCl_2$ regioselectively led to **92**, presumably via a six-membered aluminium chelate **91**. Formation of acetal **93** and DIBAL-H reduction regioselectively led to alcohol **94** which was oxidized to aldehyde **95**. For an alternative route from **86** to **93**, see Supporting Information.

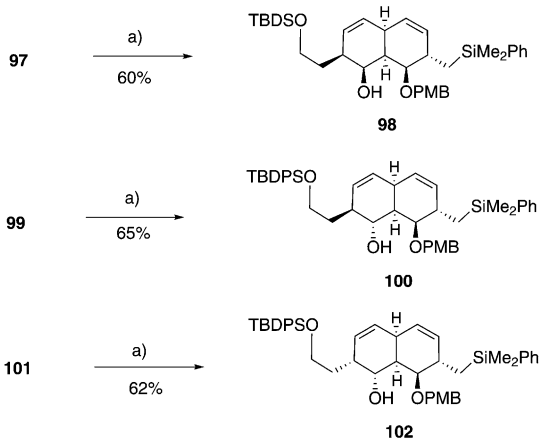


Scheme 24. Synthesis of aldehyde **95**. a) Ph_3PCH_3Br, *t*BuOK, THF, RT, 30 min, 88%; b) TBAF, THF, RT, 90%; c) $PhMe_2SiCH_2MgCl$, CuCl, PPh_3, $EtAlCl_2$, toluene, RT, 24 h, THF, 70%; d) $CH_3OC_6H_4CHO$, TsOH, benzene, $MgSO_4$, 97%; e) DIBAL-H, CH_2Cl_2, 0°C, 4 h, 78%; f) DMP, $NaHCO_3$, CH_2Cl_2, RT, 30 min, 92%.

To introduce the second double bond via Hiyama–Nozaki–Kishi reaction[48,49] aldehyde **95** was treated with allylbromide **96**[50] (Scheme 25) in presence of $CrCl_2$, to give a mixture of alcohols **97** (49%), **99** (21%) and **101** (19%) which were separated and cyclized with Grubbs' 2nd generation catalyst to provide compounds **98**, **100** and **102**, respectively, whose relative configurations were unambiguously assigned by NOE experiments (Scheme 26).[51]



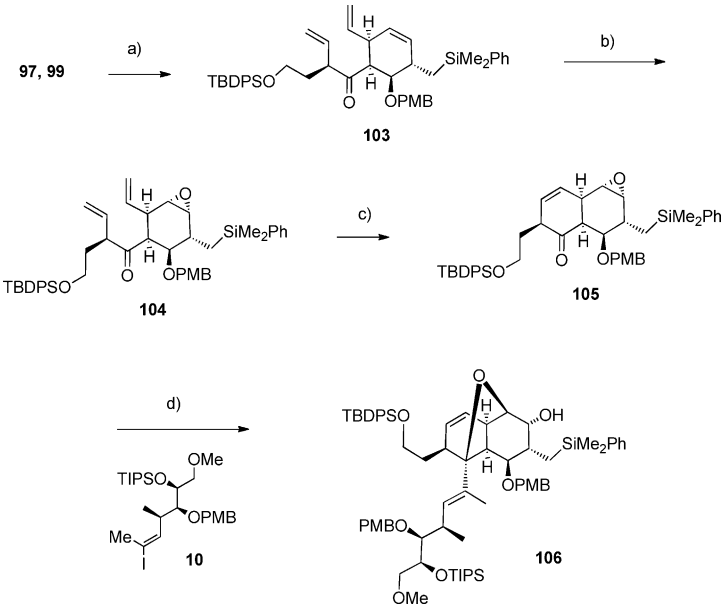
Scheme 25. Hiyama–Nozaki–Kishi reaction of aldehyde **95** with allyl bromide **96**. a) $CrCl_2$, **96**, DMF, RT, 2 h.



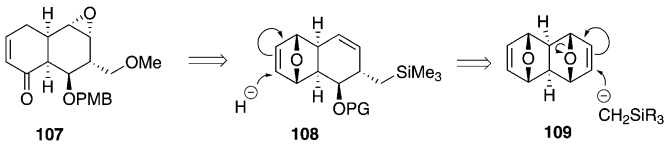
Scheme 26. RCM of **97**, **99**, **101**. a) Grubbs' second generation cat, toluene, 50°C, 2 h.

As compounds **97** and **99** turned out to be C-12 epimers, they were oxidized (Scheme 27) to ketone **103**, whose reaction with *m*CPBA afforded epoxide **104** as a single regio- and stereoisomer. RCM of **104** with Grubbs' 2nd generation catalyst provided epoxy-ketone **105**. Finally, **105** was treated with the organolithium derivative of side chain **10**. As expected, the addition to the carbonyl group was followed by transannular epoxide opening to generate ether **106**, whose configuration was confirmed by 2D NMR studies.

Encouraged by this successful desymmetrization approach we envisioned that the construction of a dehydrodecalone core such as **107** could be accomplished more rapidly by desymmetrization[52] of the known diepoxynaphthalene **109**[53] (Scheme 28) via two successive S_N2' reactions. First a copper-mediated opening of one of the oxa bridges was to be performed with $PhSiMe_2SiCH_2MgCl$ as before, to provide a racemic mixture of intermediate **108** which should be subjected to a chiral resolution by a S_N2' opening of the second oxa bridge with a chiral hydride source.



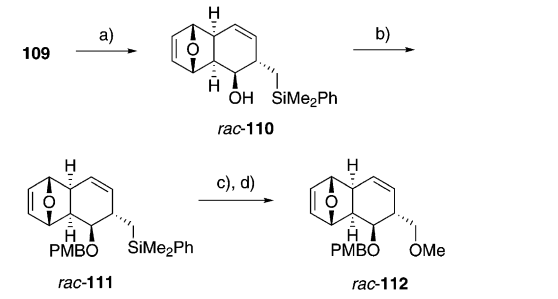
Scheme 27. Synthesis of branimycin precursor **106**. a) DMP, $NaHCO_3$, CH_2Cl_2, RT, 15 min, 95%; b) *m*CPBA, $CHCl_3$, $NaHCO_3$, −15°C, 16 h, 90%; c) Grubbs' second generation cat, toluene, 50°C, 2 h, 92%; d) **10**, *t*BuLi (1.8 M in pentane), THF, −80°C,1 h, then **105**, THF, −78°C, 3 h, 42%.



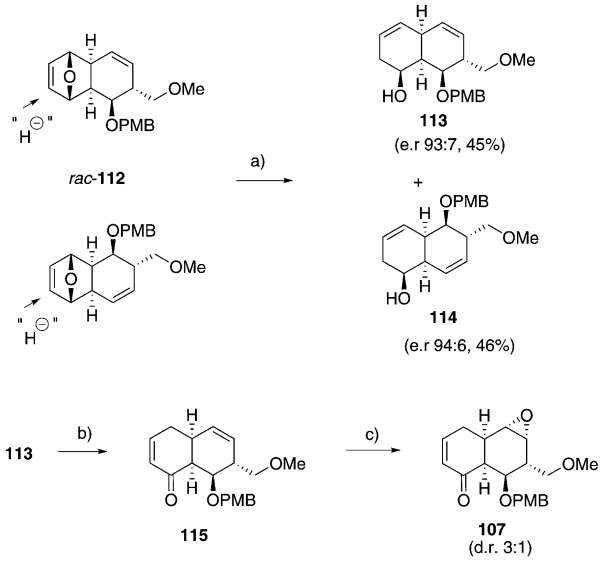
Scheme 28. Alternative desymmetrization approach.

Gratifyingly the addition of $Me_2PhSiCH_2MgCl/CuCl/Ph_3P$ to **109** resulted in an S_N2' opening of only one of the oxa bridges to give compound **110** which was protected as PMB-ether **111**. Tamao–Fleming conditions[54] to furnish the primary alcohol which was converted to methyl ether **112** in 73% yield over two steps (Scheme 29).

To perform the envisioned chiral resolution (Scheme 30) *rac*-**112** was treated with DIBAL-H and $[Ni(cod)_2]/(R)$-BINAP.[55] A pseudo-enantiotopos-selective hydride attack was observed on both enantiomers of **112** to give the enantiomerically enriched regioisomers **113**[56] and **114** in 91% yield, easily separable by chromatography. Dess–Martin oxidation of **113** provided a ketone which was surprisingly reluctant to undergo base induced double bond migration. Only under enforced conditions the conjugated enone **115** was obtained, whose regioselective epoxidation with *m*CPBA gave a 3:1 mixture of diastereomeric epoxides, easily separable by chromatography. To avoid competitive Baayer–Villiger reaction of the ketone, the reaction was stopped at about 50% conversion. The relative configuration of the major epoxide diastereomer **107** was determined by single crystal diffraction.[7h]



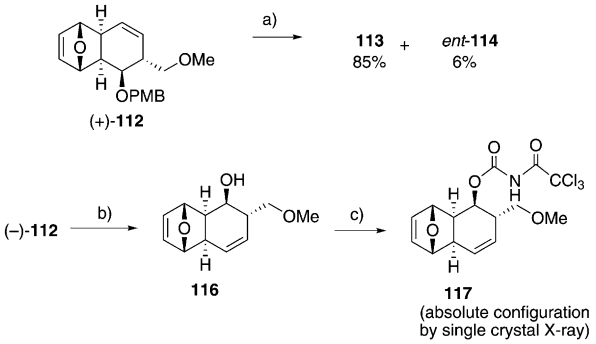
Scheme 29. Diastereoselective organometal addition to **109**. a) $Me_2PhSiCH_2MgCl$, CuCl (10 mol%), Ph_3P (10 mol%), toluene, RT, 48 h, 75% (82% brsm); b) PMBCl, NaBr, DMF, RT, 2 h; then **110**, NaH, THF, 0°C→RT, 8 h, 85% (96% brsm); c) KH, *t*BuOOH, TBAF, NMP, THF, RT, 3 h, 82%; d) MeI, NaH, THF, DMF, 0°C, 12 h, 89%.



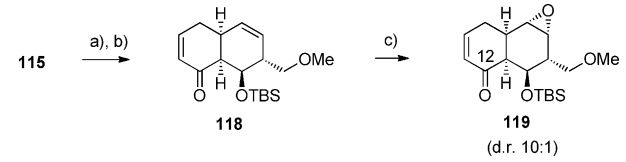
Scheme 30. Chiral resolution of **112** and conversion of **113** to epoxide **107**. a) $[Ni(cod)_2]$ (20 mol%), (*R*)-BINAP (30 mol%), DIBAL-H, toluene, RT, 6 h, 91%; b) DMP, $NaHCO_3$, CH_2Cl_2, RT, 20 min, then DBU, CH_2Cl_2, reflux, 45 min, 82%; c) *m*CPBA, CH_2Cl_2, 0°C, 50% conversion, 85%. BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

To secure the absolute configuration of our products (Scheme 31), racemic compound **112** was separated into the enantiomers by chiral HPLC. Under the same conditions used for the racemate, enantiomer (+)-**112** gave **113** along with small amounts of *ent*-**114**. On the other hand, (−)-**112** was converted into alcohol **116** and then into urethane **117**, whose absolute configuration was assigned by single crystal diffraction using the anomalous dispersion of chlorine atoms.[7h] By this set of experiments we were absolutely sure that compound **113** has the absolute configuration which had been postulated for branimycin.[6]

Carrying on with the synthesis, we tried to improve the diastereoselectivity of the epoxidation. Quite surprisingly it turned out that the distant OPMB protecting group had a pronouncedly negative influence. After changing the pro-



Scheme 31. Assignment of the absolute configuration of **113**. a) [Ni(cod)$_2$] (20 mol%), (*R*)-BINAP (30 mol%), DIBAL-H, toluene, RT, 6 h, 91%; b) DDQ, CH_2Cl_2, pH 7 buffer, 40 min, 10–20°C, 95%; c) $CCl_3C(=O)$-N=C=O, $CHCl_3$, RT, 10 min, 66%.



Scheme 32. Preparation of decalone **119**. a) DDQ, pH 7 buffer, CH_2Cl_2, 0–2°C, ultrasonic bath; b) TBSOTf, 2,6-di-*tert*-butylpyridine, THF, −78°C, 1 h, 89% for two steps; c) *m*CPBA, CH_2Cl_2, 0°C, 2 h, 60% conversion, 84% (brsm) + 8% (brsm) of the diastereomeric epoxide. TBS = *tert*-butyldimethylsilyl.

tecting group from PMB in **107** to TBS in **118**, we obtained epoxide **119** with a d.r. of 10:1 (Scheme 32).

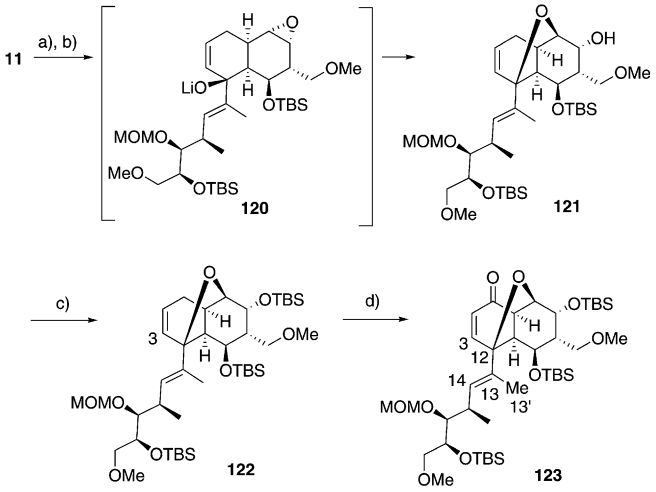
Thus far we had pursued, in a competitive, evolutionary way, five different routes to the *cis*-dehydrodecalin core of branimycin. It was now time to select the most promising one for the completion of the synthesis.

As Table 1 shows the first three approaches have serious problems. Approaches 4 and 5 are similarly favorable with respect to the number of steps and overall yield, with the advantage that in contrast to **119**, dehydrodecalone **105** is already appropriately functionalized for a Claisen rearrangement. However, we were confident that **119** could be provided with the required oxygen via allylic oxidation. In the end it was the fact that compound **119** was prepared faster and in larger quantities than **105**, that settled the issue in a "Darwinian" sense.

Table 1. Comparison of the different approaches to dehydrodecalin intermediates.

Approach#/ Decalin core	Key step/Number of steps/Yield [%]	Source of chirality	Potential
#1/**54**	TADA/10/7	L-ascorbic acid	poor
#2/**77**	INOC/13/9	quinic acid	poor
#3/**79**	RCM/14/12	quinic acid	moderate
#4/**105**	desymmetrization, RCM/ 10/16	enzymatic resolution	good
#5/**119**	desymmetrization/10/16	chiral catalyst	very good

Completion of the synthesis: From the behavior of epoxy ketone **105** we were confident that the addition of the missing side chain at C-12 of **119** could be done. Thus, vinyl iodide **11** was metalated with *tert*-butyllithium and the organolithium species was added to ketone **119** (Scheme 33). Performing the reaction at high concentration (0.5 M based on Li^+) allowed subsequent in situ opening of the epoxide by the initially formed alkoxide anion in **120**. Lower concentrations of the reaction resulted in extremely slow formation of the bridge and isolation of the tertiary alcohol resulting from the protonation of **120**. Presumably, Li^+ acts as a Lewis acid facilitating opening of the epoxide. The newly created OH functionality was protected as TBS-ether **122**.



Scheme 33. Preparation of intermediate **123**. a) **11** (1.7 equiv), *t*BuLi, THF, −78°C, 2.5 h; b) **119** (1.0 equiv), THF, −78°C, 5 min, warming to 22°C overnight, 82%; c) TBSCl, imidazole, DMF, 22°C, 12 h, 95%; d) CrO_3, 3,5-dimethylpyrazole, CH_2Cl_2, −20°C, 2 h, then **122** in CH_2Cl_2, −20°C, 2 h, 55% (+ 8% of the regioisomer).

The next task was the introduction of the C-3 side chain, for which several options were considered. An ene reaction[57] would have been an obvious choice; however, the presence of the epoxide was not promising for the application of the required Lewis acid. So we settled for the construction of an allylic alcohol or a conjugated enone, both of which would allow the introduction of a carbon appendage at C-3 either via sigmatropic rearrangement or conjugate addition.

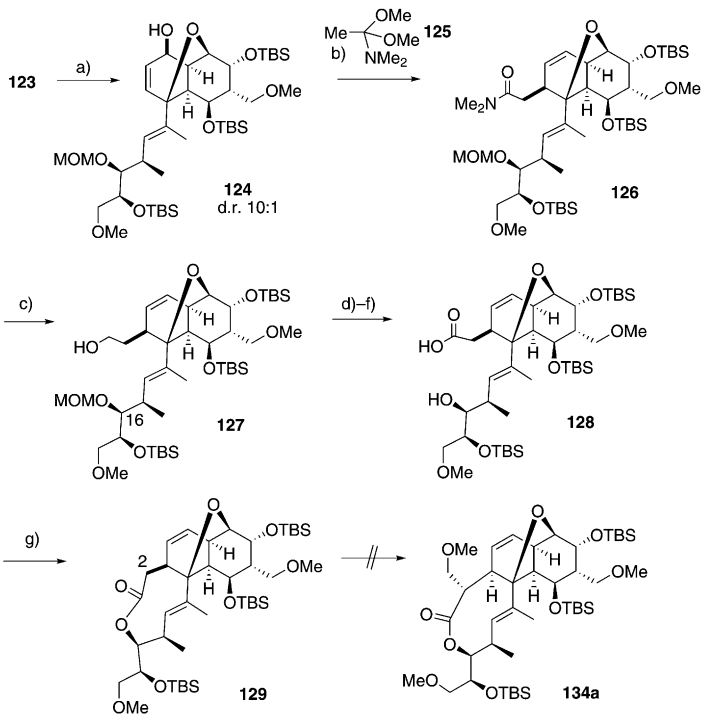
In fact, allylic oxidation[58] of **122** furnished enone **123** (Scheme 33). To introduce the side chain at C-3 via one of the Claisen-type rearrangements,[23] **123** was reduced to the allylic alcohol **124** (Scheme 34). As expected, the oxygen bridge shielded the top face of ring A efficiently, so that the hydride attack occurred from the bottom face with good stereoselectivity. Several attempts to perform a Johnson–Claisen or Ireland–Claisen reaction did not yield the desired

product. The Eschenmoser–Claisen rearrangement with acetamide acetal **125** under conventional conditions[59] also failed to give the desired amide **126** (for details see Supporting Information). This was not unexpected, as the oxygen bridge exerts a significant steric hindrance upon the top side of ring A and is clearly in the way of the desired sigmatropic rearrangement. After long experimentation, a breakthrough was achieved by using the acetamide acetal **125** as a solvent along with DMF, adding MS 4 Å and employing high temperatures and short reaction times (220 °C, 2 min) under microwave irradiation in a closed vessel. Amide **126** was now formed in 64 % yield. As direct hydrolysis of amide **126** to the acid would have required harsh conditions, we used a reduction–oxidation sequence instead. Thus, reduction with lithium triethylborohydride gave alcohol **127**. First a direct re-oxidation of **127** to the carboxylic acid was considered; however, it soon turned out that the selective deprotection of 16-OMOM in presence of the TBS groups was not possible. Therefore, the OMOM-protecting group was removed at the stage of **127**. After that, selective oxidation of the primary hydroxyl group with TEMPO[60] first to the aldehyde and then with sodium chlorite to *seco*-acid **128** paved the way for a Yamaguchi macrolactonization[61] which smoothly provided the nine-membered lactone **129**. Unfortunately the C-2 position in **129** proved totally inert towards deprotonation and thus, all attempts to attach the 2-CH_2OMe group to form **134a** were unsuccessful.

Therefore we returned to enone **123** and decided to install the crucial C-3 side chain via Michael addition (Scheme 35). This was highly risky, as the substrate directed bottom-side addition observed in the reduction of **123** to **124** should have resulted in the formation of the wrong C-3 diastereomer. Fortunately, however, enone **123** added malonate anion stereoselectively from the top face. There are two possible rationalizations of this result: a) a complexation of the sodium counterion to O-12′ which is unlikely in a solvent such as methanol; b) the conformational effect shown in Figure 5: to avoid steric strain the 13′-Me group is rotated downward into a bisectic position and thus shields the bottom face of C-3.

The resulting enolate was trapped as vinyl triflate whose reduction with Bu_3SnH under Pd catalysis gave diester **130** in good yield. Unfortunately the two diastereotopic ester functions could not be differentiated, neither via chemical saponification, nor via enzymatic lipase-catalyzed hydrolysis. Therefore they were both reduced to diol **131**, which was alkylated to a mixture of monomethyl ethers, the ratio of which strongly depended on the conditions. Thus, MeI and Ag_2O[62] furnished a 1:1 mixture, whereas the d.r. was 1:4 with MeI/KHMDS.

After selective deprotection of the OMOM group with $MgBr_2$, the diastereomers **132a/b** were readily separated and the oxidation to *seco*-acids **133a** and **b** proceeded in excellent yield. However, Yamaguchi lactonization led to elimination at the 2-CH_2OMe group, presumably induced by the base present in the reaction mixture. In contrast, the virtually neutral Corey–Nicolaou–Gerlach[63] conditions did afford



Scheme 34. Preparation of macrolactone **129**. a) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 12 h, 97 %; b) **125**, (7 equiv), DMF, microwave, 220 °C, 2 min, 64 %; c) $LiBEt_3H$ (10 equiv), THF, 0 °C, 5 h, 93 %; d) $MgBr_2{\cdot}Et_2O$, Me_2S, CH_2Cl_2, 40 °C, 12 h (70 % brsm); e) TEMPO (0.3 equiv), $PhI(OAc)_2$ (3 equiv), CH_2Cl_2, 22 °C, 2 h, 87 %; f) 2-methyl-2-butene, $NaClO_2$, NaH_2PO_4. H_2O, *t*BuOH, H_2O, 18 °C, 40 min, 85 %; g) 2,4,6,-trichlorobenzoyl chloride, *i*Pr_2NEt, DMAP, toluene, 80 °C, 4 h, 50 %. TEMPO = 2,2,6,6-tetramethylpiperidin-*N*-oxyl radical.

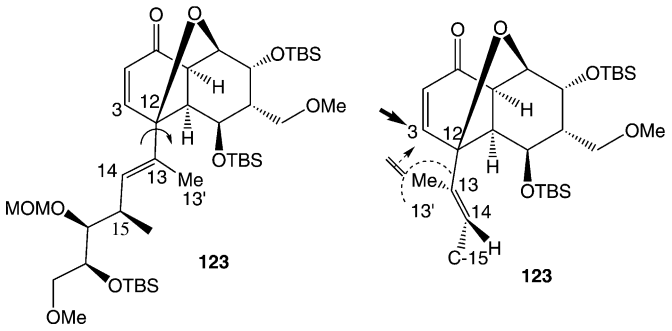
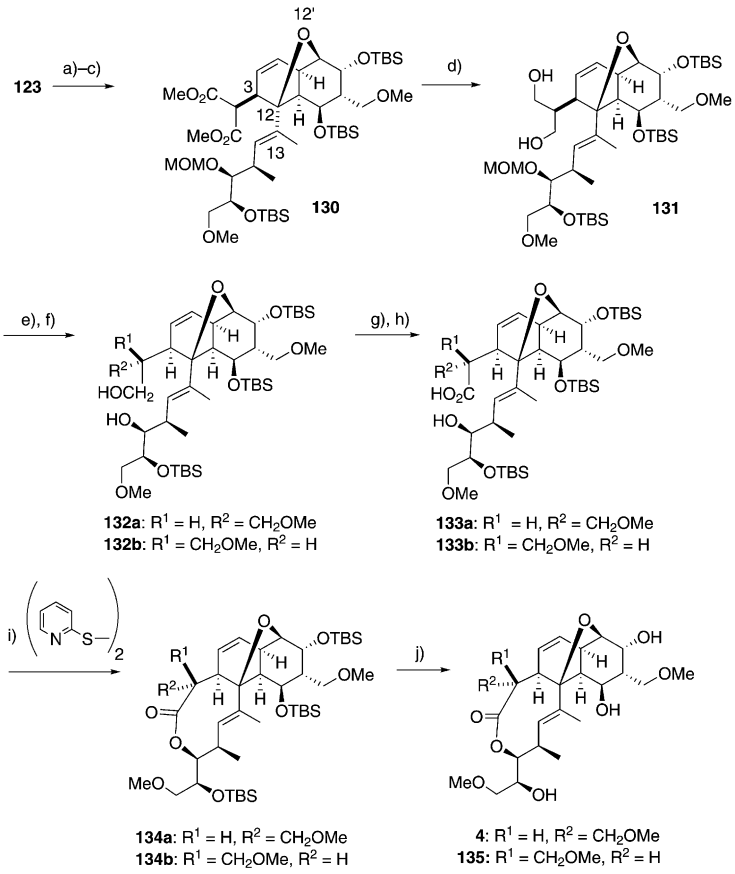


Figure 5. Conformational strain in enone **123** leads to steric shielding of the bottom face by the 13′-Me group.

the nine-membered macrolactones **134a** and **134b** in acceptable yields. On treatment with TBAF in THF the least hindered 17-OTBS group was removed first, whereupon the two remaining TBS groups followed suit to give branimycin (**4**) and its C-2 epimer **135** in high yield.[64] Our synthetic sample of **4** was indistinguishable from the authentic material (^1H and ^{13}C NMR, MS and IR spectra, optical rotation and R_f values in three different solvents)



Scheme 35. Preparation of monomethyl ethers **132a/b** and completion of the synthesis of **4**. a) $CH_2(CO_2Me)_2$, NaOMe, MeOH, −21 °C → RT, 14 h, 88 %; b) $PhNTf_2$, KHMDS, THF, −78 °C → RT, 30 min, 93 %; c) Bu_3SnH, $[Pd(PPh_3)_4]$, LiCl, 2,6-lutidine, THF, 22 °C, 14 h, 78 %; d) $LiBEt_3H$, THF, 0 °C → RT, 18 h, 85 %; e) Ag_2O, MeI, 42 °C, 24 h, 99 % (brsm); f) $MgBr_2$-Et_2O, Me_2S, CH_2Cl_2, 40 °C, 6 h, 70 % (brsm); g) TEMPO, $PhI(OAc)_2$, CH_2Cl_2, RT, 2 h, 92 %; h) 2-methyl-2-butene, $NaClO_2$, $NaH_2PO_4{\cdot}H_2O$, *t*BuOH, H_2O, 15 °C, 30 min, 90 %; i) $(PyS)_2$, PPh_3, $AgClO_4$, toluene, 85 °C, 2 h, 40 %; j) TBAF, THF, 22 °C, 14 h, 85 %.

Conclusion

In summary we have developed the first synthesis of branimycin along a convergent route with 22 steps in the longest linear sequence and an overall yield of 2 %. Our synthesis has confirmed the structural assignments made by the Laatsch group, and it has also established the absolute configuration. Typically for a project of this size, altogether five different routes to the core and three to the side chain fragments were pursued concurrently until one of them in each case emerged as the fittest. This strategy resulted in a route that is flexible with respect to the substituents and configurations of the individual stereogenic centers. More specifically, some of the hydroxyl groups might be inverted, removed or replaced by other functions, for example amines. This should lead to a sufficiently diverse library for detailed SAR studies, which are currently pursued in our laboratory.

Experimental Section

The following section describes only some representative key experiments. A full contiguous account of the experimental work including general information and copies of the ^{1}H- and ^{13}C NMR spectra are recorded in the Supporting Information.

TADA Approach

(2*R*,3*aS*,4*Z*,6*E*,8*Z*,13*E*,14*aS*)-2-Methoxy-3,3a-dihydrofuro[2,3-*e*,1]oxacyclotridecin-12(2*H*,10*H*,14*aH*)-one (39): A 250 mL Schlenk flask was charged with freshly distilled THF (140 mL). The solvent was degassed in three freeze/pump/thaw cycles. From this volume, THF (3 mL) was removed to dissolve *seco*-compound **38** (100 mg, 0.15 mmol). To the main volume $[Pd(PPh_3)_4]$ (34 mg, 0.03 mmol) and LiCl (9.4 mg, 0.22 mmol) was added, followed by **38** dissolved in THF. After 5 min, $Bu_4NPh_2PO_2$ (135 mg, 0.29 mmol) was added. The solution was then heated to 40 °C for 3 h, after which another $[Pd(PPh_3)_4]$ (10 mg) and LiCl (4 mg) were added, and the reaction stirred at 40 °C for 18 h. The reaction mixture was filtered over a pad of Celite and the solvent removed under reduced pressure. The residue was redissolved in hexanes and washed with saturated $NaHCO_3$ solution. After separation of the organic layer, the aqueous layer was extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$ and then concentrated under reduced pressure. Purification by column chromatography (hexanes/EtOAc 10:1 to 7:1) yielded **39** as a colorless oil (25 mg, 65 %). $[\alpha]_D^{20} = -57.0$ ($c = 1.33$, CH_2Cl_2); R_f (hexanes/EtOAc 3:1) = 0.53; ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.85$ (dd, $J = 16.0$, 6.8 Hz, 1H), 6.26–5.95 (m, 4H), 5.87 (d, $J = 16.1$ Hz, 1H), 5.59 (m, 1H), 5.35 (dd, $J = 10.2$ Hz, 1H), 5.14 (dd, $J = 5.7$, 3.9 Hz, 1H), 4.92 (dd, $J = 15.0$, 5.3 Hz, 1H), 4.72 (br d, $J = 15.0$ Hz, 1H), 4.18 (dd, $J = 9.7$, 9.0 Hz, 1H), 3.40 (s, 3H), 2.75 (m, 1H), 2.52 (ddd, $J = 13.5$, 9.0, 5.7 Hz, 1H), 1.76 ppm (ddd, $J = 13.5$, 9.7, 3.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.2$ (C), 147.1 (CH), 131.8 (CH), 130.4 (CH), 129.1 (CH), 128.9 (CH), 128.8 (CH), 126.6 (CH), 120.9 (CH), 106.1 (CH), 80.7 (CH), 61.6 (CH_2), 55.6 (CH_3), 46.9 (CH), 40.0 ppm (CH_2); IR (Si, film): $\tilde{\nu}$ = 2930, 1725, 1654, 1622, 1577, 1496, 1449, 1372, 1340, 1243, 1214, 1154, 1099, 1028, 981, 952, 914, 858, 768, 744, 670 cm^{-1}; MS (EI): *m*/*z*: 262 (45) [M^+], 231 (6), 183 (29), 162 (91); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{18}O$: 262.1205; found: 262.1212.

(2*R*,3*aR*,5*aR*,7*aS*,10*aS*,10*bS*,10*cR*)-2-Methoxy-2,3,3a,7a,8,10a,10b,10c-octahydro-5a*H*-1,9-dioxa-dicyclopenta[*a*,*h*]naphthalene-10-one (20): Macrolactone **39** (20 mg, 0.07 mmol) and BHT (5 mg, 0.02 mmol) were dissolved in xylenes (3 mL) and heated to reflux for 24 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography (hexanes/EtOAc 2:1) to yield **20** (white solid (14 mg, 70 %) and **21** (1.4 mg, 7 %) as a colorless oil.

20: m.p. 114–118 °C; $[\alpha]_D^{20} = -24.6$ ($c = 1.64$, CH_2Cl_2); R_f (hexanes/EtOAc 1:1) = 0.36; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.76$ (br d, $J = 9.6$ Hz, 1H), 5.63 (br d, $J = 10.2$ Hz, 1H), 5.54 (br d, $J = 9.8$ Hz, 1H), 5.52 (ddd, $J = 9.8$, 3.6, 3.6 Hz, 1H), 5.15 (dd, $J = 5.2$ Hz, 1H), 4.38 (dd, $J = 8.8$, 5.7 Hz, 1H), 4.14 (d, $J = 8.8$ Hz, 1H), 3.51 (dd, $J = 11.7$, 9.6 Hz, 1H), 3.40 (s, 3H), 3.22 (dd, $J = 6.9$, 2.4 Hz, 1H), 3.18 (m, 1H), 3.06 (m, 1H), 2.73 (ddd, $J = 11.6$, 6.8, 2.5 Hz, 1H), 2.44 (ddd, $J = 12.5$, 7.4, 5.5 Hz, 1H), 2.35 (m, 1H), 1.51 ppm (ddd, $J = 12.5$, 12.5, 4.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 172.9$ (C), 131.9 (CH), 130.1 (CH), 125.3 (CH), 123.6 (CH), 106.6 (CH), 77.5 (CH), 72.1 (CH_2), 55.8 (CH_3), 44.1 (CH), 38.9 (CH), 37.3 (CH_2), 35.8 (CH), 34.9 (CH), 32.7 ppm (CH); IR (Si, film): $\tilde{\nu}$ = 3021, 2917, 2849, 1771, 1546, 1454, 1369, 1211, 1162, 1107, 1088, 1070, 1030, 1000, 967, 937, 906, 858, 757, 728, 680, 517 cm^{-1}; MS (EI): *m*/*z*: 262 (61) [M^+], 230 (68), 204, (100); HRMS (EI): *m*/*z*: calcd for $C_{15}H_{18}O$: 262.1205; found: 262.1210.

(2*R*,3*aSKaS*,7*aR*,10*aR*,10*bR*,10*cR*)-2-Methoxy-2,3,3a,7a,8,10a,10b,10c-octahydro-5a*H*-1,9-dioxadicyclopenta[*a*,*h*]naphthalen-10-one (21): R_f (hexanes/EtOAc 1:1) = 0.33; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 5.91$ (ddd, $J = 9.9$, 5.6, 2.4 Hz, 1H), 5.79 (ddd, $J = 9.6$, 1.9, 1.9 Hz, 1H), 5.65 (ddd, $J = 9.9$, 1.7, 1.7 Hz, 1H), 5.53 (ddd, $J = 9.6$, 3.9, 2.8 Hz, 1H), 5.14 (dd, $J = 5.3$, 4.8 Hz, 1H), 4.34 (dd, $J = 8.7$, 5.7 Hz, 1H), 4.12 (dd, $J = 9.1$, 2.7 Hz, 1H), 3.85 (dd, $J = 10.1$, 6.0 Hz, 1H), 3.42 (s, 3H), 3.17 (m, 1H), 3.02 (ddd, $J = 7.4$, 6.0, 4.2 Hz, 1H), 2.95 (dd, $J = 7.0$, 4.2 Hz, 1H), 2.92 (m, 1H), 2.45

(dd, $J=12.7$, 7.4, 5.4 Hz, 1H), 2.30 (m, 1H), 1.52 ppm (dd, $J=12.7$, 5.0 Hz, 1H).

Quinic acid approach, INOC reaction of 66 to 68

(1*S*,3a^1*R*,5a*S*,6*S*,6a*R*,8*S*,9*S*,10a*R*,10b*S*)-8,9-Dimethoxy-1-((4-methoxybenzyl)oxy)-6-(methoxymethyl)-8,9-dimethyl-3a^1,5a,6,6a,8,9,10a,10b-octahydro-1*H*-[1,4]dioxino[2′,3′:5,6]naphtho[1,8*cd*]isoxazole (68): A solution of **66** (0.61 g, 1.24 mmol), NCS (0.168 g, 1.26 mmol) and pyridine (72 μL) in chloroform (20 mL) was heated for 10 min at 40 °C and for 1 h at 60 °C. After removing the solvent under reduced pressure water (50 mL) was added and the mixture was extracted with CH_2Cl_2 (3× 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography to give **68** (0.56 g, 92 %). ^{1}H NMR (400 MHz, $CDCl_3$): (branimycin numbering): $\delta=7.26$ (d, $J=$ 8.6 Hz, 2H, H(ar)), 6.87 (d, $J=8.6$ Hz, 2H, H(ar)), 6.60 (d, $J=10.0$ Hz, 1H, H-3), 6.40 (dd, $J=10.0$, 5.3 Hz, 1H, H-4), 4.97 (d, $J=10.6$ Hz, 1H, H-10), 4.56 (d, $J=11.2$ Hz, 1H, OCH_2(ar)), 4.52 (d, $J=11.2$ Hz, 1H, OCH_2(ar)), 4.42 (dd, $J=5.3$, 1.6 Hz, 1H, H-5), 4.03 (dd, $J=10.8$, 10.6), Hz, 1H, H-7), 3.89 (dd, $J=10.6$, 4.5 Hz, 1H, H-8), 3.80 (s, 3H, CH_3O(ar)), 3.74 (dd, $J=10.6$, 6.7 Hz, 1H, H-11), 3.53 (dd, $J=9.5$, 3.9 Hz, 1H H-20), 3.42 (dd, $J=9.5$, 6.7 Hz, 1H, H-20), 3.33 (s, 3H, CH_3O(20)), 3.14 (s, 3H, CH_3O(7)), 3.09 (s, 3H, CH_3O(8)), 2.96 (ddd, $J=10.8$, 6.7, 1.6 Hz, 1H, H-6), 2.14 (m, 1H, H-9), 1.17 (s, 3H, CH_3), 1.12 ppm (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=159.38$ (s), 156.67 (s), 135.55 (d), 130.33 (s), 129.38 (2xd), 119.56 (d), 113.88 (2xd), 100.33 (s), 99.90 (s), 80.28 (d), 70.95 (t), 69.12 (d), 68.69 (t), 65.99 (d), 65.21 (d), 58.91 (q), 55.29 (q), 47.56 (q), 47.52 (q), 44.10 (d), 42.48 (d), 35.16 (d), 17.66 (q), 17.63 ppm (q).

Desymmetrization approach, completion of the synthesis

(1*R,4*S**,4a*S**,5*S**,6*S**,8a*S**)-6-((Dimethyl(phenyl)silyl)methyl)-1,4,4a,5,6,8a-hexahydro-1,4-epoxynaphthalen-5-ol (*rac*-110)**

Grignard reagent: A dry, 100 mL, two-necked, round-bottomed flask was equipped with a septum and a reflux condenser, the top of which was connected to an argon line. The flask was charged with magnesium turnings (0.84 g, 35 mmol) and dry diethyl ether (40 mL) and immersed into an ultrasound bath at 32–35 °C. To the sonicated mixture was added dibromoethane (0.05 mL) and then a solution of $PhMe_2SiCH_2Cl$ (10 g, 30 mmol) in dry diethyl ether (10 mL) was added in a rate keeping the reaction mixture at reflux (ca. 1 h). At the end of the addition the mixture was kept in the ultrasound bath at reflux for additional 1 h.

Oxa-bridge opening: CuCl (153 mg, 1.54 mmol) and Ph_3P (444 mg, 1.69 mmol) in dry toluene (160 mL) were sonicated in an ultrasonic bath at 20–40 °C for ca. 1 h until a milky white opalescent solution was formed. Diepoxynaphthalene **109** (2.5 g, 15.4 mmol) was added and the mixture was further sonicated for additional 30 min to obtain a fine suspension. The flask was removed from the ultrasonic bath, charged with a stirring bar and the reaction mixture was cooled to r.t. under stirring. Then a solution of the Grignard reagent (30 mmol) was added, and the reaction mixture was stirred for 48 h at RT until no more progress could be observed (TLC). The reaction mixture was quenched with saturated NH_4Cl (100 mL) and stirred for 2 h. The water phase was separated and extracted with CH_2Cl_2 (2×30 mL). The combined organic phases were washed with brine, passed through a plug of cotton and concentrated in vacuo to dryness. (NOTE: If required, the residue can be directly subjected to flash column chromatograph (SiO_2, EtOAc/toluene, then EtOAc/CH_2Cl_2 to elute **4**)). The crude product was stirred with Et_2O (75 mL), and filtered from the insoluble residue (mostly contains **109**). The filtrate was concentrated in vacuo to dryness and triturated with hexane (50 mL) for 2 h. The resulting white crystals were filtered, washed with hexane (2×10 mL) and dried in vacuo to obtain a mixture of **110** (3.1–3.5 g) and **109** (5–10 mol %). The hexane fraction was concentrated in vacuo and the residue was subjected to column chromatography (EtOAc/toluene, then EtOAc/CH_2Cl_2 to elute **109**) to get pure **110** (ca. 0.3–0.7 g). The yield of **110** was 3.60 g (75 %, 82 % brsm).

110: m.p. 94–95 °C; ^{1}H NMR (400 MHz): $\delta=7.54$–7.49 (m, 2H), 7.37–7.33 (m, 3H), 6.40 (dd, $J=1.5$, 5.8 Hz, 1H), 6.35 (dd, $J=1.5$, 5.8 Hz, 1H), 5.76 (dd, $J=2.5$, 10.0 Hz, 1H), 5.72 (ddd, $J=1.7$, 4.1, 10.0 Hz, 1H), 5.05 (brs, 1H), 4.65 (brs, 1H), 3.83 (ddd, $J=5.5$, 5.5, 7.6 Hz, 1H), 2.66 (brd, $J=$ 7.6 Hz, 1H, *OH*), 2.50–2.41 (m, 1H), 2.13 (brd, $J=8.2$ Hz, 1H), 2.08 (dd, $J=5.5$, 8.2 Hz, 1H), 0.96 (dd, $J=4.2$, 14.4 Hz, 1H), 0.96 (dd, $J=10.7$, 14.4 Hz, 1H), 0.33 (s, 3H), 0.32 ppm (s, 3H); ^{13}C NMR (100.6 MHz): $\delta=$ 139.5, 136.6, 135.4, 133.8, 133.6, 129.1, 128.2, 128.0, 83.6, 79.6, 73.5, 39.0, 38.0, 37.7, 19.6, −1.8, −2.2 ppm; IR (Si, film): $\tilde{\nu}=3468$, 2930, 820 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{21}H_{27}NNaO_2Si$ $[M+Na+CH_3CN]^+$: 376.1709; found: 376.1717.

(((1*R,4*S**,4a*S**,5*S**,6*S**,8a*S**)-5-((4-Methoxybenzyl)oxy)-1,4,4a,5,6,8a-hexahydro-1,4-epoxynaphthalen-6-yl)methyl)dimethyl(phenyl)silane (*rac*-111)**

Solution of PMBBr in DMF: Dry NaBr (3.44 g, 33.4 mmol) was suspended in dry DMF (8 mL) at 25 °C, PMBCl (2.62 g, 16.7 mmol) was added and the reaction mixture was stirred for 2 h at 25 °C. NMR analysis showed ca. 90 % conversion. (NOTE*:* extension of the reaction time did not result in improvement of conversion.)

PMB protection: A stirred solution of PMBBr in DMF (prepared from 16.7 mmol of PMBCl, ca. 15.0 mmol) was diluted with DMF (10 mL), cooled to 0 °C and NaH (60 % in mineral oil, 0.61 g, 15.2 mmol) was added. A solution of **110** (2.40 g, 7.6 mmol) in DMF (11 mL) was added within 5 min and stirring was continued for 6 h at 0 °C and 2 h at RT. Then $NH_2CH_2CH_2NH_2$ (5 mL) was added and the mixture was stirred for 1 h at 0 °C and 1 h at RT until no more PMBBr and PMBCl could be detected by TLC. Volatiles were removed in vacuo at RT, the reaction mixture was diluted with EtOAc (200 mL) and washed repeatedly with 1N HCl until pH 5–6 was reached. The combined water phases were extracted with EtOAc (3×100 mL). The combined organic phases were washed with water (3×100 mL), brine (50 mL) and passed through a plug of cotton. Solvents were removed in vacuo and the residue was subjected to flash column chromatography (EtOAc/hexane) to give **111** (clear oil; 2.75 g, 85 %, 96 % brsm) and **110** (0.31 g, 13 %). (NOTE*:* Extension of reaction times did not improve conversion. Equal results were obtained when pure PMBBr was used instead of material prepared in situ.)

111: ^{1}H NMR (400 MHz): $\delta=7.56$–7.50 (m, 2H), 7.36–7.31 (m, 3H), 7.28 (brd, $J=8.7$ Hz, 2H), 6.89 (brd, $J=8.7$ Hz, 2H), 6.32 (d, $J=1.6$, 5.8 Hz, 2H), 6.25 (d, $J=1.6$, 5.8 Hz, 2H), 5.64 (ddd, $J=2.8$, 4.8, 9.9 Hz, 1H), 5.72 (dd, $J=1.3$, 9.9 Hz, 1H), 5.07 (brs, 1H), 4.65 (brs, 1H), 4.54 (d, $J=$ 11.6 Hz, 1H), 4.44 (d, $J=11.6$ Hz, 1H), 3.82 (s, 3H), 3.31 (dd, $J=6.1$, 9.8 Hz, 1H), 2.53 (bdd, $J=10.4$, 10.4 Hz, 1H), 2.23–2.18 (m, 1H), 2.05 (dd, $J=6.3$, 7.6 Hz, 1H), 1.44 (dd, $J=3.02$, 14.7 Hz, 1H), 0.59 (dd, $J=$ 11.1, 14.7 Hz, 1H), 0.33 (s, 3H), 0.20 ppm (s, 3H); ^{13}C NMR (100.6 MHz): $\delta=159.2$, 140.4, 137.7, 134.8, 134.4, 133.7, 131.4, 129.3, 128.8, 127.8, 127.4, 113.9, 85.4, 83.9, 78.3, 71.4, 55.4, 39.5, 39.2, 34.8, 19.0, −1.71, −1.73 ppm; IR (Si, film): $\tilde{\nu}=2952$, 1612, 1513, 1248, 836 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{27}H_{32}NaO_3Si$ $[M+Na]^+$: 455.2018; found: 455.2012.

((1*R,4*S**,4a*S**,5*R**,6*R**,8a*S**)-5-((4-Methoxybenzyl)oxy)-1,4,4a,5,6,8a-hexahydro-1,4-epoxynaphthalen-6-yl)methanol**: KH (30 wt % suspension in mineral oil, 0.83 g, 20.8 mmol) was placed in a dried 200 mL flask under Ar. Mineral oil was removed by washing the suspension with dry hexane (3×5 mL), *N*-methyl-2-pyrrolidone (NMP, 25 mL) was added and the flask was cooled to 0 °C. Under vigorous stirring *t*BuOOH (5–6 M in decane, 4.2 mL, ≥20.8 mmol) was added dropwise over 10 min, followed by addition of a solution of **110** (1.50 g, 3.5 mmol) in NMP (10 mL) over 5 min The reaction mixture was warmed to RT, TBAF (1 M in THF, 7.5 mL, 7.5 mmol) was added and the stirring was continued for 3 h. The reaction mixture was quenched with aq. $Na_2S_2O_3$ (5 M, 50 mL), stirred for 30 min, diluted with water (1 L) and extracted EtOAc/toluene 2:1 (5× 200 mL). The combined organic phase was washed with water (2× 200 mL), brine (200 mL) and dried over $MgSO_4$. Solvents were removed in vacuo and the residue was subjected to a flash column chromatography (toluene/EtOAc) to yield the alcohol as a colorless oil (0.89 g, 82 %). ^{1}H NMR (400 MHz): $\delta=7.30$ (brd, $J=8.8$ Hz, 2H), 6.90 (brd, $J=8.8$ Hz, 2H), 6.38 (dd, $J=1.7$, 5.8 Hz, 1H), 6.31 (dd, $J=1.6$, 5.8 Hz, 1H), 5.86–5.81 (m, 1H), 5.47 (dd, $J=1.5$, 9.9 Hz, 1H), 5.14 (brs, 1H), 4.71 (brs, 1H), 4.64 (d, $J=11.3$ Hz, 1H), 4.49 (d, $J=11.3$ Hz, 1H), 3.81 (s, 3H), 3.73 (dd, $J=6.5$, 10.5 Hz, H), 3.63 (dd, $J=7.3$, 10.5 Hz, 1H), 2.64–2.56 (m, 1H), 2.32–2.67 (m, 1H), 2.17 ppm (dd, $J=6.2$, 7.6 Hz, H); ^{13}C NMR (100.6 MHz): $\delta=159.4$, 137.4, 134.9, 130.1, 129.7, 129.4, 129.0, 114.0, 85.4, 81.2, 77.9, 70.6, 66.2, 55.3, 40.1, 39.2, 38.8 ppm; IR (Si, film): $\tilde{\nu}=3460$,

3822, 3676, 3651, 3629, 3448, 2931, 1701, 1513, 1249, 1033, 821 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{19}H_{22}NaO_4$ $[M+Na]^+$ 337.1416; found: 337.1412.

(1*R,4*S**,4a*S**,5*R**,6*R**,8a*S**)-5-((4-Methoxybenzyl)oxy)-6-(methoxymethyl)-1,4,4a,5,6,8a-hexahydro-1,4-epoxynaphthalene (*rac*-112)**: To a suspension of NaH (60% in mineral oil, 300 mg, 7.6 mmol) in dry THF (12 mL) at 0°C was added dry DMF (12 mL) and MeI (5.4 g, 2.5 mL, 38 mmol), followed by the abovementioned alcohol (1.2 g, 3.8 mmol) in dry THF (5 mL). The reaction mixture was stirred at 0°C for 12 h. Then saturated aq. NH_4Cl (1 mL) was added carefully and the volatiles were removed in vacuo at RT (**CAUTION***:* distillate contains MeI, which is toxic!). The residue was diluted with water (70 mL) and extracted with toluene (5×50 mL). The combined organic phase was washed with water (3×20 mL), brine (30 mL) and passed through a plug of cotton. The solvents were removed in vacuo and the residue was subjected to column chromatography (EtOAc/hexane) to yield 1.11 g of *rac*-**112** (89%) as a colorless oil. ^{1}H NMR (400 MHz): δ=7.30 (br d, J=8.8 Hz, 2H), 6.90 (br d, J=8.8 Hz, 2H), 6.38 (dd, J=1.6, 5.8 Hz, 2H), 6.28 (dd, J=1.5, 5.8 Hz, 1H), 5.83 (ddd, J=2.9, 4.6, 9.9 Hz, 1H), 5.71 (dd, J=1.5, 9.9 Hz, H), 5.14 (br s, 1H), 4.68 (br s, 1H), 4.57 (d, J=11.4 Hz, 1H), 4.50 (d, J=11.4 Hz, 1H), 3.81 (s, 3H), 3.74 (d, J=6.3, 10.4 Hz, 1H), 3.58 (d, J=4.5, 9.0 Hz, 1H), 3.50 (d, J=3.0, 9.0 Hz, 1H), 3.33 (s, 3H), 2.57–2.49 (m, 1H), 2.29–2.23 (m, 1H), 2.08 ppm (br t, 1H); ^{13}C NMR (100.6 MHz): δ=159.3, 137.7, 134.9, 131.2, 130.8, 129.5, 129.1, 113.9, 85.6, 78.2, 76.8, 72.8, 71.4, 59.2, 55.4, 39.4, 39.4, 39.3 ppm; IR (Si, film): $\tilde{\nu}$ = 2928, 1612, 1513, 1249, 1117, 1079, 822 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{24}NaO_4$ $[M+Na]^+$ 351.1572; found: 351.1570.

(1*S*,4a*S*,7*R*,8*R*,8a*R*)-8-((4-Methoxybenzyl)oxy)-7-(methoxymethyl)-1,2,4a,7,8,8a-hexahydronaphthalen-1-ol (113) and (1*R*,4a*S*,5*S*,6*R*,8a*S*)-5-((4-methoxybenzyl)oxy)-6-(methoxymethyl)-1,2,4a,5,6,8a-hexahydronaphthalen-1-ol (114): A solution of $[Ni(cod)_2]$ (420 mg, 1.52 mmol) in toluene (dry and degassed; 25 mL) was added to (*R*)-BINAP (1.43 g, 2.29 mmol) and the mixture was stirred at RT for 4 h. (NOTE*:* the solution became dark burgundy red. Green or brown colors indicate presumably a partial oxidation of Ni^0 species and may result in lower selectivity.) To this burgundy red solution a solution of *rac*-**112** (2.50 g, 7.62 mmol) in toluene (43 mL) was added (the color stayed dark burgundy red, but a weak green-brown shade appeared) and the mixture was stirred for 30 min Then DIBAL-H (1.0 M in hexanes, 8.8 mL, 8.8 mmol) was added over 6 h at 22°C via a syringe pump. The reaction was allowed to stir for 1 h, then saturated aq. sodium potassium tartrate (100 mL) was added and the mixture was stirred for 30 min The organic phase was separated and the water phase was extracted with Et_2O (4×50 mL). The combined organic phase was washed with brine, passed through a plug of cotton and the solvents were removed in vacuo. The solid residue was triturated with MeOH (50 mL), the solution was filtered to remove undissolved BINAP and its oxides, and the filtrate was concentrated in vacuo. The residue was subjected to flash column chromatography (EtOAc/hexane) to obtain **114** (1.16 g, 46%) as yellowish crystals and a mixture of **113** with (*R*)-BINAP monooxide. The latter mixture was resubjected to flash column chromatography (EtOAc/toluene) to yield **113** (1.13 g, 45%) as a colorless oil. $[\alpha]_D^{20}$ = +146.2 (c=1.10, $CHCl_3$); ^{1}H NMR (400 MHz): δ= 7.29 (br d, J=8.9 Hz, 2H), 6.88 (br d, J=8.9 Hz, 2H), 5.80–5.74 (m, 1H), 5.69–5.58 (m, 3H), 4.58 (d, J=11.4 Hz, 1H), 4.43 (d, J=11.4 Hz, 1H), 4.45–4.39 (m, 1H), 3.81 (dd, J=5.3, 9.7 Hz, 1H), 3.81 (s, 3H), 3.53–3.46 (m, 2H), 3.30 (s, 3H), 3.06–2.98 (m, 1H), 2.98–2.91 (m, 1H), 2.39–2.34 (m, 1H), 2.26–2.22 (m, 2H), 1.90 ppm (d, J=10.3 Hz, 1H, *OH*); ^{13}C NMR (100.6 MHz): δ=159.3, 131.0, 129.5, 128.8, 128.7, 128.5, 123.6, 113.9, 75.5, 73.3, 70.9, 64.2, 59.1, 55.4, 40.5, 37.5, 35.2, 34.8 ppm; IR (Si, film): $\tilde{\nu}$ = 3480, 2890, 1513, 1247, 772 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{20}H_{26}NaO_4$ $[M+Na]^+$: 353.1729; found: 353.1733.

114: m.p. 104–106°C; $[\alpha]_D^{20}$ = −151.3 (c = 1.6, $CHCl_3$); ^{1}H NMR (400 MHz): δ=7.25 (br d, J=8.7 Hz, 2H), 6.87 (br d, J=8.7 Hz, H), 5.79–5.74 (m, 1H), 5.72–5.66 (m, 2H), 5.64–5.59 (m, 1H), 4.56 (d, J=11.3 Hz, 1H), 4.47 (d, J=11.3 Hz, 1H), 4.00–3.94 (m, 1H), 3.79 (s, 3H), 3.69 (dd, J=3.6, 6.5 Hz, 1H), 3.45–3.33 (m, 2H), 3.31 (s, 3H), 2.91–2.84 (m, 1H), 2.69–2.63 (m, 1H), 2.26–2.10 (m, 2H); ^{13}C NMR (100.6 MHz): δ=159.3, 130.3, 129.6, 128.3, 126.2, 113.9, 75.7, 73.6, 71.2, 67.7, 59.0, 55.4, 40.5, 39.8, 36.0, 32.4 ppm; IR (Si, film): $\tilde{\nu}$ = 3400, 2874, 1612, 1514, 1248, 1077, 671 cm^{-1}.

Malonate addition to 125

Dimethyl 2-((1*S*,2*R*,4a*R*,5*R*,6*R*,7*R*,8*R*,8a*S*)-6,8-bis((*tert*-butyldimethylsilyl)oxy)-1-((4*R*,5*S*,6*S*,*E*)-6-((*tert*-butyldimethylsilyl)oxy)-7-methoxy-5-(methoxymethoxy)-4-methylhept-2-en-2-yl)-7-(methoxymethyl)-4-oxodecahydro-1,5-epoxynaphthalen-2-yl)malonate: To a solution of Na (6 mg, 0.263 mmol) in MeOH (0.8 mL) was added dimethyl malonate (0.18 mL, 1.579 mmol) at RT and the resulting mixture was stirred for 5 min. This mixture was then cooled to - 21°C and a solution of enone **125** (140 mg, 0.175 mmol) in MeOH (0.8 mL) was added. The mixture was warmed to RT overnight, then diluted with Et_2O and quenched with aq. saturated NH_4Cl. The water phase was extracted with Et_2O (3×3 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated in vacuo to give a residue, which was purified by flash chromatography (EtOAc/hexane) on silica gel to afford 144 mg (88%) of the Michael adduct as an oil. $[\alpha]_D^{20}$ = +42.4 (c=0.55, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ=5.88 (d, J=10.0 Hz, 1H), 4.76 (d, J=6.6 Hz, 1H), 4.69 (d,J=6.6 Hz, 1H), 4.02–3.94 (m, 3H), 3.68 (s, 3H), 3.66 (s, 3H), 3.58 (d, J=2.6 Hz, 1H), 3.56 (dd, J=11.2, 2.5 Hz, 1H), 3.51 (dd, J=9.5, 4.7 Hz, 1H), 3.44 (dd, J=4.6, 4.6 Hz, 1H), 3.42 (s, 3H), 3.38 (dd, J=9.5, 6.4 Hz, 1H), 3.34 (s, 3H), 3.32–3.26 (m, 2H), 3.22 (s, 3H), 3.10 (dd, J= 17.4, 7.2 Hz, 1H), 3.04 (s, 1H), 2.94–2.87 (m, 2H), 2.87–2.80 (m, 1H), 2.56 (dd, J=17.4, 8.7 Hz, 1H), 2.42 (d, J=2.4 Hz, 1H), 1.71 (d, J= 1.1 Hz, 1H), 1.04 (d, J=7.0 Hz, 1H), 0.91 (s, 9H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 6H), 0.03 (s, 3H), 0.00 ppm (s, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ=208.5, 169.6, 169.2, 133.0, 129.6, 100.1, 98.4, 89.8, 83.0, 80.9, 75.0, 73.3, 71.4, 69.9, 68.8, 58.9, 58.6, 55.9, 53.4, 52.8, 52.0, 49.6, 49.4, 42.2, 41.1, 37.1, 33.3, 26.3, 26.1, 26.0, 18.4, 18.3, 18.2, 16.7, 15.9, −3.2, −4.2, −4.4, −4.5, −5.3 ppm; IR (Si, film): $\tilde{\nu}$ = 2928, 2851, 1792, 1735, 1539, 1473, 1307, 1254, 1177, 1118, 1060, 1028, 949, 837, 794, 777, 676, 420, 418, 416, 403 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{46}H_{86}O_{13}Si_3Na$ $[M+Na]^+$: 953.5274; found: 953.5291.

Macrolactonization of *seco*-acids 133a and b

(3*R*,4*S*,7*R*,7a*R*,9a*R*,10*R*,11*R*,12*R*,13*R*,13a*S*,13b*S*,*E*)-11,13-Bis((*tert*-butyldimethylsilyl)oxy)-4-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)-2-methoxyethyl)-7,12-bis(methoxymethyl)-1,3-dimethyl-7,7a,9a,10,11,12,13,13a-octahydro-3*H*-10,13b-epoxynaphtho[2,1-*d*]oxonin-6(4*H*)-one (134b): To *seco*-acid **133a** (6 mg, 0.007 mmol) was added a solution of 2,2′-dithiodipyridine (0.43 M in toluene, 150 μL, 0.064 mmol) and a solution of PPh_3 (0.43 M in toluene, 150 μL, 0.064 mmol), and the mixture was stirred at RT for 14 h. The resulting mixture was diluted by toluene (5 mL) and added via syringe pump to a solution of $AgClO_4$ (44 mg, 0.214 mmol) in toluene (15 mL) at 85°C over 2 h. The resulting mixture was filtrated through a pad of celite and the filtrate was concentrated in vacuo. The residue was subjected to column chromatography (EtOAc/hexanes) to obtain lactone **134a** (2.4 mg, 40%). In the same manner **134b** was prepared from **133b**.

134a: $[\alpha]_D^{20}$ = +173.3 (c=0.05, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ= 5.98 (ddd, J=9.2, 7.0, 2.0 Hz, 1H), 5.66 (dd, J=7.5, 1.0 Hz, 1H), 5.38 (dd, J=9.8, 2.5 Hz, 1H), 4.95 (dd, J=9.2, 6.2 Hz, 1H), 4.13 (ddd, J=8.9, 7.1, 2.0 Hz, 1H), 4.03–3.97 (m, 2H), 3.69 (dd, J=11.2, 1.8 Hz, 1H), 3.58–3.51 (m, 2H), 3.46 (dd, J=8.6, 5.1 Hz, 1H), 3.41–3.33 (m, 2H), 3.33–3.25 (m, 1H), 3.31 (s, 3H), 3.29 (s, 3H), 3.24 (s, 3H), 3.07 (dm, J=9.5 Hz, 1H), 3.03–2.94 (m, 1H), 2.85–2.77 (m, 1H), 2.69 (d, J=7.0 Hz, 1H), 2.60–2.51 (m, 1H), 2.27 (s, 1H), 1.68 (s, 3H), 1.21 (d, J=6.9 Hz, 3H), 0.90 (s, 18H), 0.89 (s, 9H), 0.13 (s, 3H), 0.11 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 ppm (s, 6H); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ=177.9, 138.5, 134.2, 131.2, 127.1, 89.1, 84.2, 80.7, 76.0, 73.7, 72.5, 71.1, 70.3, 69.2, 59.2, 58.7, 58.4, 52.4, 50.0, 46.3, 41.1, 40.1, 32.3, 29.9, 26.4, 26.3, 26.0, 18.6, 18.5, 18.2, 17.4, 15.8, −3.5, −3.6, −4.3, −4.9, −5.1, −5.2 ppm; IR (Si, film): $\tilde{\nu}$ = 2955, 2929, 2857, 1721, 1472, 1389, 1361, 1252, 1211, 1116, 1084, 1057, 1031, 866, 837, 777, 668, 418, 404 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{43}H_{80}O_9Si_3Na$ $[M+Na]^+$: 847.5008; found: 847.5018.

134b:^{1}H NMR (400 MHz, $CDCl_3$): δ=5.99 (ddd, J=9.3, 6.8, 2.4 Hz, 1H), 5.74 (dd, J=9.6, 1.0 Hz, 1H), 5.46 (dd, J=9.4, 2.4 Hz, 1H), 4.98 (dd, J= 7.2, 5.1 Hz, 1H), 4.15 (dd, J=10.1, 5.3 Hz, 1H), 4.06–3.98 (m, 2H), 3.95 (dd, J=4.8, 3.9 Hz, 1H), 3.64 (dd, J=11.3, 2.1 Hz, 1H), 3.50–3.47 (m,

2H), 3.44 (dd, $J=10.1$, 2.0 Hz, 1H), 3.39–3.28 (m, 3H), 3.35 (s, 3H), 3.31 (s, 3H), 3.20 (s, 3H), 2.97–2.87 (m, 1H), 2.65 (d, $J=6.8$ Hz, 1H), 2.62–2.56 (m, 1H), 2.55–2.46 (m, 1H), 2.30 (d, $J=2.0$ Hz, 1H), 1.68 (d, $J=1.0$ Hz, 3H), 1.19 (d, $J=7.0$ Hz, 3H), 0.92 (s, 9H), 0.90 (s, 9H), 0.88 (s, 9H), 0.1 (s, 3H), 0.09 (s, 3H), 0.06 (s, 6H), 0.05 (s, 3H), 0.01 ppm (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=174.6$, 135.6, 134.3, 131.1, 130.8, 90.7, 85.2, 79.1, 75.8, 72.3, 71.9, 70.1, 69.4, 68.8, 59.2, 58.6, 58.2, 52.8, 51.3, 50.5, 40.7, 39.9, 32.6, 26.5, 26.2, 26.0, 18.5, 18.5, 18.2, 17.3, 15.5, −3.4, −3.7, −4.3, −5.0, −5.2 ppm.

(3*R*,4*S*,7*R*,7a*R*,9a*R*,10*R*,11*R*,12*R*,13*R*,13a*S*,13b*S*,*E*)-11,13-Dihydroxy-4-((*S*)-1-hydroxy-2-methoxyethyl)-7,12-bis(methoxymethyl)-1,3-dimethyl-7,7a,9a,10,11,12,13,13a-octahydro-3*H*-10,13b-epoxynaphtho[2,1-*d*]oxonin-6(4*H*)-one (branimycin) (4): To a stirred solution of lactone **134a** (1.6 mg, 0.002 mmol) in THF (0.15 mL) was added TBAF (1 M in THF, 35 μL) dropwise. The reaction mixture was then stirred for 14 h. The resulting mixture was diluted with THF and the reaction was quenched by addition of aq. saturated NH_4Cl. The water phase was extracted with EtOAc (4×1 mL), the combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The crude product was subjected to column chromatography (CCl_4/*i*PrOH) to yield branimycin (**4**) (0.8 mg, 85%) as a colorless oil. In the same manner **135** was prepared from **134b**.

4: $R_f=0.27$ ($CHCl_3$/5% MeOH), 0.22 (CCl_4/12.5% *i*PrOH), 0.35 (CH_2Cl_2/10% *i*PrOH) (R_f values identical with authentic material); $[\alpha]_D^{25}=+88.0$ ($c=0.04$, $CHCl_3$) (authentic material: $[\alpha]_D^{25}=+80.0$ ($c=0.045$, $CHCl_3$)); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta=6.05$ (ddd, $J=9.6$, 7.2, 2.0 Hz, 1H), 5.68 (dd, $J=8.0$, 1.2 Hz, 1H), 5.39 (dd, $J=9.7$, 2.2 Hz, 1H), 5.04 (dd, $J=10.0$, 6.7 Hz, 1H), 4.12–4.04 (m, 3H), 4.02 (ddd, $J=11.1$, 5.3, 2.9 Hz, 1H), 3.78 (dd, $J=9.6$, 4.6 Hz, 1H), 3.64 (dd, $J=9.6$, 5.2 Hz, 1H), 3.59–3.54 (m, 2H), 3.48 (dd, $J=8.5$, 4.8 Hz, 1H), 3.42–3.39 (m, 1H), 3.40 (s, 3H), 3.36 (s, 3H), 3.32 (s, 3H), 3.06–3.03 (m, 2H), 2.99 (d, $J=2.6$ Hz, 1H), 2.91–2.84 (m, 1H), 2.72 (d, $J=7.2$ Hz, 1H), 2.49 (d, $J=4.3$ Hz, 1H), 2.48 (d, $J=2.5$ Hz, 1H), 2.32–2.27 (m, 1H), 2.09 (d, $J=5.5$ Hz, 1H), 1.69 ppm (d, $J=0.9$ Hz, 3H), 1.27 (d, $J=7.0$ Hz, 3H); ^{13}C NMR (150.9 MHz, $CDCl_3$): $\delta=177.6$, 138.7, 133.8, 131.5, 126.8, 88.7, 84.0, 79.4, 74.6, 73.7, 73.3, 72.0, 71.9, 68.1, 59.4, 59.3, 59.3, 51.8, 48.3, 46.2, 40.4, 38.6, 32.5, 17.0, 15.4 ppm; (A comparison with authentic material is found in the Supporting Information.) IR (Si, film): $\tilde{\nu}$ = 3455, 2930, 1725, 1651, 1540, 1375, 1224, 1118, 944, 886, 874, 793, 685, 672, 668, 425, 421, 413 cm^{-1}; HRMS (ESI): *m*/*z*: calcd for $C_{25}H_{38}O_9Na$ $[M+Na]^+$: 505.2414; found: 505.2420.

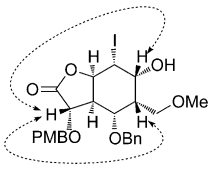
135: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=6.08$ (ddd, $J=9.5$, 6.8, 2.2 Hz, 1H), 5.66 (dd, $J=9.8$, 1.1 Hz, 1H), 5.49 (dd, $J=9.6$, 2.2 Hz, 1H), 5.04 (dd, $J=8.4$, 2.8 Hz, 1H), 4.17–4.10 (m, 2H), 4.08–3.97 (m, 3H), 3.75 (dd, $J=9.6$, 4.6 Hz, 1H), 3.63 (dd, $J=9.6$, 5.2 Hz, 1H), 3.50–3.41 (m, 3H), 3.41–3.37 (m, 1H), 3.40 (s, 3H), 3.35 (s, 3H), 3.32 (s, 3H), 3.06–2.97 (m, 1H), 2.92 (d, $J=2.7$ Hz, 1H), 2.71 (d, $J=7.0$ Hz, 1H), 2.67 (dm, $J=10.4$ Hz, 1H), 2.54 (d, $J=2.7$ Hz, 1H), 2.27–2.20 (m, 1H), 2.18–2.12 (m, 1H), 2.08 (d, $J=5.5$ Hz, 1H), 1.72 (d, $J=0.8$ Hz, 3H), 1.29 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$): $\delta=177.6$, 137.9, 136.8, 134.9, 130.0, 88.8, 82.9, 79.0, 74.9, 73.7, 73.4, 72.1, 71.9, 70.0, 59.5, 59.3, 58.8, 52.2, 48.9, 45.4, 40.6, 38.5, 33.0, 17.1, 15.6 ppm.

Acknowledgements

This research has been funded by the Austrian Science Fund (FWF) under project number P15929-N08. We thank Professor H. Laatsch (University of Göttingen) for an authentic sample of branimycin and numerous discussions, H. Kählig and L. Brecker for NMR assistance, J.-L. Mieusset for DFT calculations, V. B. Arion for X-ray analysis and M. Drescher (all University of Vienna) for experimental work.

[1] W. D. Celmer, W. P. Cullen, C. E. Moppett, M. T. Jefferson, L. H. Huang, R. Shibakawa, J. Tone, United States Patent US 4418883, **1979**.
[2] W. D. Celmer, G. N. Chmurny, C. E. Moppett, R. S. Ware, P. C. Watts, E. B. Whipple, *J. Am. Chem. Soc.* **1981**, *103*, 4203–4209.
[3] B. J. Magerlein, R. J. Reid, *J. Antibiot.* **1982**, *35*, 254–255.
[4] H. A. Whaley, C. G. Chidester, S. A. Mizsak, R. J. Wnuk, *Tetrahedron Lett.* **1980**, *21*, 3659–3662.
[5] a) W. D. Celmer, W. P. Cullen, C. E. Moppett, M. T. Jefferson, L. H. Huang, R. Shibakawa, J. Tone, United States Patent US 4224314, **1980**; b) J. K. Sohng, T. Yamaguchi, C. N. Seong, K. S. Baik, S. C. Park, H. J. Lee, S. Y. Jang, J. R. Simkhada, J. C. Yoo, *Arch. Pharm. Res.* **2011**, *31*, 1339–1345.
[6] M. Speitling, *Dissertation*, Universität Göttingen (Germany), **1998**.
[7] Preliminary reports on our synthesis: a) V. S. Enev, M. Drescher, H. Kaehlig, J. Mulzer, *Synlett* **2005**, 2227–2229; b) W. Felzmann, V. B. Arion, J.-L. Mieusset, J. Mulzer, *Org. Lett.* **2006**, *8*, 3849–3851; c) J. Mulzer, D. Castagnolo, W. Felzmann, S. Marchart, C. Pilger, V. S. Enev, *Chem. Eur. J.* **2006**, *12*, 5992–6001; d) S. Marchart, J. Mulzer, V. S. Enev, *Org. Lett.* **2007**, *9*, 813–816; e) W. Felzmann, D. Castagnolo, D. Rosenbeiger, J. Mulzer, *J. Org. Chem.* **2007**, *72*, 2182–2186; f) V. S. Enev, M. Drescher, J. Mulzer, *Tetrahedron* **2007**, *63*, 5930–5939; g) V. S. Enev, M. Drescher, J. Mulzer, *Org. Lett.* **2008**, *10*, 413–416; h) A. Gromov, V. S. Enev, J. Mulzer, *Org. Lett.* **2009**, *11*, 2884–2886; i) S. Marchart, A. Gromov, J. Mulzer, *Angew. Chem.* **2010**, *122*, 2094–2097; *Angew. Chem. Int. Ed.* **2010**, *49*, 2050–2053.
[8] a) D. J. Plata, J. Kallmerten, *J. Am. Chem. Soc.* **1988**, *110*, 4041–4042; b) J. Kallmerten, D. J. Plata, *Heterocycles* **1987**, *25*, 145–149; c) L. T. Rossano, D. J. Plata, J. Kallmerten, *J. Org. Chem.* **1988**, *53*, 5189–5191.
[9] a) W. R. Roush, K. Koyama, M. L. Curtin, K. J. Moriarty, *J. Am. Chem. Soc.* **1996**, *118*, 7502–7512; b) E. Gössinger, A. Schwartz, N. Sereinig, *Tetrahedron* **2001**, *57*, 3045–3061 and references therein.
[10] J. Kallmerten, *Tetrahedron Lett.* **1984**, *25*, 2843–2846.
[11] R. F. Jones, J. H. Tunnicliffe, *Tetrahedron Lett.* **1985**, *26*, 584–5848.
[12] a) W. R. Roush, J. W. Coe, *Tetrahedron Lett.* **1987**, *28*, 931–934; b) J. W. Coe, W. R. Roush, *J. Org. Chem.* **1989**, *54*, 915–930.
[13] Some reviews on IMDA and TADA reactions: a) K. C. Nicolaou, S. A. Snyder, T. Montagnon, G. Vassilikogiannakis, *Angew. Chem.* **2002**, *114*, 1742–1773; *Angew. Chem. Int. Ed.* **2002**, *41*, 1668–1698; b) G. R. Stephenson, *Chem. Ind.* **2004**, *6*, 28–29; c) K. Takao, R. Munakata, K. Tadano, *Chem. Rev.* **2005**, *105*, 4779–4807; d) M. Juhl, D. Tanner, *Chem. Soc. Rev.* **2009**, *38*, 2983–2992.
[14] Some recent TADA examples in natural product synthesis: a) S. Phoenix, M. S. Reddy, P. Deslongchamps, *J. Am. Chem. Soc.* **2008**, *130*, 13989–13995; b) M. Tortosa, N. A. Yakelis, W. R. Roush, *J. Org. Chem.* **2008**, *73*, 9657–9667; c) N. Hayashi, T. Suzuki, K. Usui, M. Nakada, *Tetrahedron* **2009**, *65*, 888–895; d) H. Takamura, Y. Yamagami, T. Ito, M. Ito, H. Arimoto, I. Kadota, D. Uemura, *Heterocycles* **2009**, *77*, 351–364; e) M. E. Jung, T.-H. Zhang, R. M. Lui, O. Gutierrez, K. N. Houk, *J. Org. Chem.* **2010**, *75*, 6933–6940; f) Y. Li, G. Pattenden, *Tetrahedron Lett.* **2011**, *52*, 2088–2092.
[15] Gaussian 03 (Revision C.02), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Wallingford CT, **2004**, was used for these calculations.
[16] a) G. Stork, K. Zhao, *Tetrahedron Lett.* **1982**, *23*, 2173–2174; b) S. Ma, X. Lu, Z. Li, *J. Org. Chem.* **1992**, *57*, 709–713.

[17] S. Masamune, W. R. Roush, T. Sakai, *Tetrahedron Lett.* **1984**, *25*, 2183–2186.
[18] J. K. Stille, *J. Am. Chem. Soc.* **1986**, *108*, 3033–3040.
[19] A. Sorg, R. Brückner, *Synlett* **2005**, 289–293.
[20] P. R. Blakemore, *J. Chem. Soc. Perkin Trans. 1* **2002**, 2563–2585.
[21] J. Srogl, G. D. Allred, L. S. Liebeskind, *J. Am. Chem. Soc.* **1997**, *119*, 12376–12377.
[22] An earlier INOC approach was unsuccessful, see ref. [7c], some reviews on INOC: a) K. E. Larsen, K. G. B. Torsell, *Tetrahedron* **1984**, *40*, 2985–2988; b) P. de La Cruz, E. Espildora, J. J. Garcia, A. de La Hoz, F. Langa, N. Martin, L. Sanchez, *Tetrahedron Lett.* **1999**, *40*, 4889–4892; c) P. Caramella, P. Grunanger, *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley-Interscience, New York, NY, **1984**, pp. 291; d) V. Jäger, P. A. Colinas, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products* (Eds.: A. Padwa, W. H. Pearson), Wiley, New Jersey, NJ, **2003**, pp. 361; e) C. C. Browder, *Curr. Org. Synth.* **2011**, *8*, 628–644.
[23] Review on Claisen Rearrangements: *The Claisen Rearrangement* (Eds.: M. Hiersemann, U. Nubbemeyer), Wiley-VCH, Weinheim, **2007**.
[24] T. Mukaiyama, M. Hayashi, *Chem. Lett.* **1974**, 15–16.
[25] S. Murata, M. Suzuki, R. Noyori, *Tetrahedron* **1988**, *44*, 4259–4275.
[26] L. M. Murray, P. O'Brien, R. J. K. Taylor, *Org. Lett.* **2003**, *5*, 1943–1946.
[27] S. D. Burke, W. F. Fobare, G. J. Pacofsky, *J. Org. Chem.* **1983**, *48*, 5221–5228 and references therein, see also ref. [23].
[28] W. C. Still, C. Gennari, *Tetrahedron Lett.* **1983**, *24*, 4405–4408.
[29] D. P. Curran, *J. Am. Chem. Soc.* **1983**, *105*, 5826–5833.
[30] A. P. Kozikowski, *Acc. Chem. Res.* **1984**, *17*, 410–416.
[31] D. P. Curran, *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026.
[32] S. H. Jung, E. K. Lee, H. J. Sung, S. O. Kim, *Bull. Korean Chem. Soc.* **1996**, *17*, 2–4.
[33] J. W. Bode, N. Fraefel, D. Muri, E. M. Carreira, *Angew. Chem.* **2001**, *113*, 2128–2131; *Angew. Chem. Int. Ed.* **2001**, *40*, 2082–2085.
[34] M. Nitta, T. Kobayashi, *J. Chem. Soc. Chem. Commun.* **1982**, 877–878.
[35] B. H. Kim, P. B. Jacobs, R. L. Elliott, D. P. Curran, *Tetrahedron* **1988**, *44*, 3079–3092.
[36] Some reviews: a) H.-G. Schmalz, *Angew. Chem.* **1995**, *107*, 1981–1984; *Angew. Chem. Int. Ed. Eng.* **1995**, *34*, 1833–1836; b) R. H. Grubbs, S. Chang, *Tetrahedron* **1998**, *54*, 4413–4450; c) S. K. Armstrong, *J. C. S. Perkin Trans. 1* **1998**, 371–388; d) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140–3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012–3043; e) C. W. Lee, R. H. Grubbs, *Org. Lett.* **2000**, *2*, 2145–2147; f) T. M. Trinka, R. H. Grubbs, *Acc. Chem. Res.* **2001**, *34*, 18–29; g) T. Gaich, J. Mulzer, *Curr Top. Med. Chem.* **2005**, *5*, 1473–1494; h) V. Bohrsch, S. Blechert, *ChiuZ* **2005**, *39*, 379–380; i) W. H. C. Martin, S. Blechert, *Curr. Top. Med. Chem.* **2005**, *5*, 1521–1540; j) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem.* **2005**, *117*, 4564–4601; *Angew. Chem. Int. Ed.* **2005**, *44*, 4490–4527; k) A. Gradillas, J. Perez-Castells, *Angew. Chem.* **2006**, *118*, 6232–6247; *Angew. Chem. Int. Ed.* **2006**, *45*, 6086–6101; l) A. Szadkowska, K. Grela, *Curr. Opin. Chem. Biol. Curr. Top. Org. Chem.* **2008**, *12*, 1631–1647; m) J. Cossy, S. Arseniyadis, C. Meyer, R. H. Grubbs, *Metathesis in Natural Product Synthesis: Strategies, Substrates and Catalysts*, Wiley-VCH, Weinheim, **2010**; n) M. Yu, C. Wang, A. F. Kyle, P. Jakubec, D. J. Dixon, R. R. Schrock, A. H. Hoveyda, *Nature* **2011**, *479*, 88–89.
[37] E. J. Corey, A. Gross, *Tetrahedron Lett.* **1984**, *25*, 495–498.
[38] Selected NOE data for iodolactone .



[39] O. Mitsunobu, *Synthesis* **1981**, *1*, 1–28.
[40] Based on 86% yield for the **2** Claisen–Ireland rearrangement after one recycling step.
[41] R. H. Grubbs, B. Schwab, J. W. Ziller, *J. Am. Chem. Soc.* **1996**, *118*, 100–110.
[42] a) S. B. Garber, J. S. Kingsbury, B. L. Gray, A. H. Hoveyda, *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179; b) S. Gessler, S. Randl, S. Blechert, *Tetrahedron Lett.* **2000**, *41*, 9973–9976.
[43] M. Lautens, S. R. Ma, K. Belter, P. Chiu, A. Leschziner, *J. Org. Chem.* **1992**, *57*, 4065–4066.
[44] For other examples of transition metal-catalyzed opening of oxabicyclic alkenes see: a) M. Lautens, K. Fagnou, S. Hiebert, *Acc. Chem. Res.* **2003**, *36*, 48–58; b) M. Lautens, S. Hiebert, *J. Am. Chem. Soc.* **2004**, *126*, 1437–1447 and references therein; c) M. Nakamura, A. Hirai, E. Nakamura, *J. Am. Chem. Soc.* **2000**, *122*, 978–979; d) M. Nakamura, K. Matsuo, T. Inoue, E. Nakamura, *Org. Lett.* **2003**, *5*, 1373–1375.
[45] R. G. Arrayas, S. Cabrera, J. C. Carretero, *Org. Lett.* **2003**, *5*, 1333–1336.
[46] G. Mandville, C. Girard, R. Bloch, *Tetrahedron: Asymmetry* **1997**, *8*, 3665–3673.
[47] a) C. Cinquin, I. Shaper, G. Mandville, R. Bloch, *Synlett* B, 339–340; b) K. Takao, H. Yasui, S. Yamamoto, D. Sasaki, S. Kawasaki, G. Watanabe, K. Tadano, *J. Org. Chem.* **2004**, *69*, 8789–8795.
[48] a) Y. Okude, S. Hirano, T. Hiyama, H. Nozaki, *J. Am. Chem. Soc.* **1977**, *99*, 3179–3180; b) Y. Okude, T. Hiyama, H. Nozaki, *Tetrahedron Lett.* **1977**, *18*, 3829–3832.
[49] Reviews: a) K. Takai, H. Nozaki, *Proc. Jpn. Acad. Ser. B* **2000**, *76B*, 123–131; b) A. Fürstner, *Chem. Rev.* **1999**, *99*, 991–1045; c) L. A. Wessjohann, G. Scheid, *Synthesis* **1999**, 1–36; d) M. Avalos, R. Babiano, P. Cintas, J. L. Jimenez, J. C. Palacios, *Chem. Soc. Rev.* **1999**, *28*, 169–177.
[50] Prepared according to: K. C. Nicolaou, D. E. Lizos, D. W. Kim, D. Schlawe, R. G. Noronha, D. A. Longbottom, M. Rodriquez, M. Bucci, G. Cirino, *J. Am. Chem. Soc.* **2006**, *128*, 4460–4470.
[51] It has to be pointed out that although the RCM reaction was quantitative, attempts to subject compounds **98**, **100** and **102** to chromatography in a presence of air resulted in a substantial loss of the material most probably via oxidation of the skipped diene system.
[52] For similar desymmetrizations, see: a) M. Lautens, E. Fillion, *J. Org. Chem.* **1996**, *61*, 7994–7995; b) M. Lautens, E. Fillion, *J. Org. Chem.* **1998**, *63*, 647–656.
[53] a) A. Gromov, V. S. Enev, J. Mulzer, *Synth. Commun.* **2010**, *40*, 104–110; b) L. Maksimovic, N. Novak, M. Eckert-Maksic, *Synth. Commun.* **1993**, *23*, 3119–3125.
[54] a) I. Fleming, R. Henning, H. E. Plaut, *J. Chem. Soc. Chem. Commun.* **1984**, 29–31; b) K. Tamao, N. Ishida, T. Tanaka, M. Kumada, *Organometallics* **1983**, *2*, 1694–1696; c) I. Fleming, R. Henning, D. C. Parker, H. E. Plaut, P. E. J. Sanderson, *J. Chem. Soc. Perkin Trans. 1* **1995**, 317–337.
[55] M. Lautens, T. Rovis, *Tetrahedron* **1998**, *54*, 1107–1116.
[56] Toluene as a solvent was essential for a high yield of the desired products. Performing the reaction in THF resulted in much lower regioselectivity. This solvent effect might be attributed to the higher Lewis acidity of aluminum species in the non-coordinating toluene. An increase in Lewis acidity presumably favors coordination of Al with the oxa-bridge and therefore facilitates the C–O bond cleavage. For other examples of Lewis acids influence on oxa-bridges opening see: M. Lautens, P. Chiu, S. Ma, T. Rovis, *J. Am. Chem. Soc.* **1995**, *117*, 532–533 and references therein.
[57] a) B. B. Snider, *Acc. Chem. Res.* **1980**, *13*, 426–432; b) K. Mikami, M. Shimizu, *Chem. Rev.* **1992**, *92*, 1021–1050; c) M. Johannsen, K. A. Jorgensen, *J. Org. Chem.* **1995**, *60*, 5757–5762; d) J. S. Johnson, D. A. Evans, *Acc. Chem. Res.* **2000**, *33*, 325–335; e) M. R. Pitts, J. Mulzer, *Tetrahedron Lett.* **2002**, *43*, 8471–8473; f) D. A. Evans, L. Kaerno, T. B. Dunn, A. Beauchemin, B. Raymer, J. A. Mulder, E. J. Olhava, M. Juhl, K. Kagechika, D. A. Favor, *J. Am. Chem. Soc.* **2008**, *130*, 16295–16309.
[58] W. G. Salmond, M. A. Rarta, J. L. Havens, *J. Org. Chem.* **1978**, *43*, 2057–2059.
[59] A. E. Wick, D. Felix, K. Steen, A. Eschenmoser, *Helv. Chim. Acta* **1964**, *47*, 2425–2429.
[60] A. E. J. de Nooy, A. C. Besemer, H. van Bekkum, *Synthesis* **1996**, *10*, 1153–1174.

[61] J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, M. Yamaguchi, *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989–1993.
[62] A. Bouzide, G. Sauve, *Tetrahedron Lett.* **1997**, *38*, 5945–5948.
[63] H. Gerlach, A. Thalmann, *Helv. Chim. Acta* **1974**, *57*, 2661–2663.
[64] The relative configurations at C-2 in **134a**, **b**, **4** and **135** were safely assigned by NOE experiments.

Received: January 24, 2012
Published online: July 4, 2012

