Natural Product Synthesis

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α-Oxygenated Crotyltitanium and Dyotropic Rearrangement in the Total Synthesis of Discodermolide**

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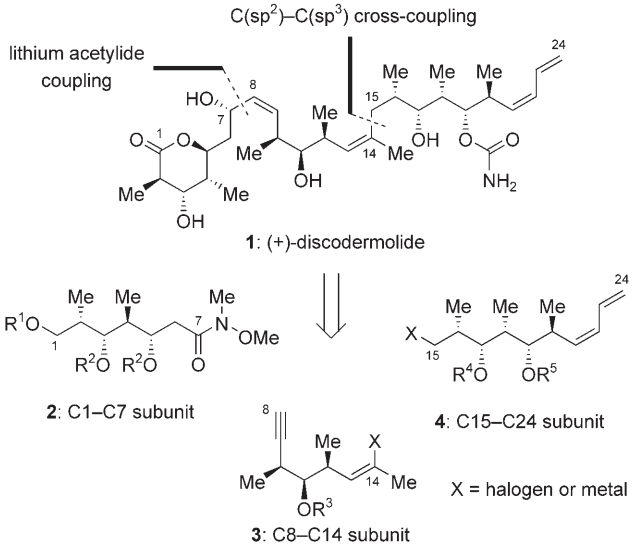
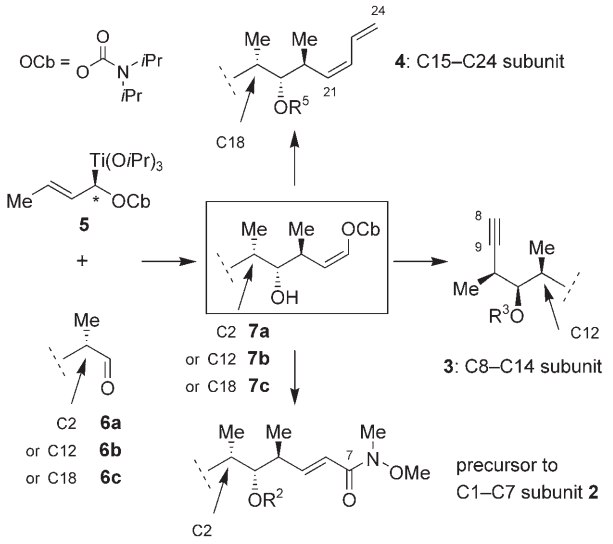
Discodermolide is a polyketide natural product that was first isolated in 1990 from extracts of the rare Caribbean marine sponge *Discodermia dissoluta* by Gunasekera et al.[1] This compound has been shown to inhibit the proliferation of cells by arresting the G_2/M phase of the cell cycle.[2] Discodermolide belongs to the class of antimitotic agents known to act by microtubule stabilization, whose members used clinically include taxol and taxotere. This product is more potent in stabilizing microtubules, more water-soluble than taxoid compounds, and exhibits synergy with taxol.[3] The marine sponge cannot provide the quantities of discodermolide needed for drug development. Therefore, efficient and highly convergent syntheses are needed, and studies in the area are increasing.[4]

Herein, we report a new total synthesis of discodermolide that relies on three particular points: elaboration of *syn–anti* stereotriads linked to a *Z*-*O*-enecarbamate group, direct transformation of this core into the terminal *Z* diene, and stereocontrolled generation of the trisubstituted *Z* double bond by dyotropic rearrangement. Our convergent synthetic strategy, which is outlined in Scheme 1, relies on the preparation of the three subunits C1–C7 (**2**), C8–C14 (**3**), and C15–C24 (**4**).[4h] Each subunit, or its precursors, possesses a *syn–anti* methyl–hydroxy–methyl triad (in C2–C4, C12–C10, and C18–C20, respectively, for fragments **2**, **3**, and **4**) with adjacent unsaturation (Scheme 2). Therefore, we developed a convenient and scalable elaboration of this core motif. A crotyltitanation reaction, developed by Hoppe[5] and widely used in total synthesis by us,[6] was selected.



Scheme 1. Retrosynthetic analysis of discodermolide (**1**).



Scheme 2. Preparation of the *syn–anti* methyl–hydroxy–methyl triad cores and subsequent use of the *Z*-*O*-enecarbamate function.

The enantioenriched (*R*)-α-(*N*,*N*-diisopropylcarbamoyloxy)crotyltitanium (**5**) was readily prepared in situ from crotyl diisopropylcarbamate, an equimolar mixture of *n*BuLi/(−)-sparteine, and tetra(isopropoxy)titanium.[7] Matched reactions between α-(*S*)-methyl aldehydes **6a–c** and *R*-

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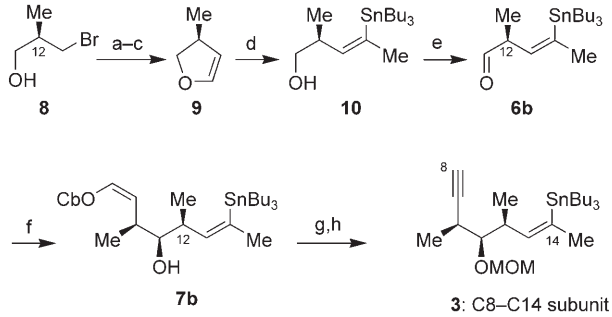
crotyltitanium **5** should yield homoaldol adducts **7a–c** with high diastereoselectivities. The stereocenters of these alcohols have the correct absolute configurations linked to a *Z*-*O*-enecarbamate group.

Moreover, we wanted to take advantage of this *Z*-*O*-enecarbamate function to set up the required unsaturation. The alkyne function in C8–C9 of subunit **3** could result from a carbenoid rearrangement, the α,β-unsaturated Weinreb amide in C7 of subunit **2** from a cross-metathesis reaction, and the terminal *Z* diene in C21–C24 of subunit **4** from a nickel-catalyzed cross-coupling reaction. For this strategy, we had to prepare suitable aldehydes for each subunit.

The crucial central subunit **3** possesses the C13–C14 trisubstituted *Z* double bond and a terminal alkyne group. The C8–C9 triple bond should be accessible by an *O*-enecarbamate rearrangement. For stereocontrolled building of the C13–C14 trisubstituted functionalized *Z* double bond, we considered focusing on a dyotropic rearrangement of 5-lithiodihydrofuran, which was first examined by Fujisawa[8] and developed by Kocienski[9] and us.[10] This attractive reaction should allow the construction of various trisubstituted *Z* or *E* double bonds, in good yields and with total control of their geometry.

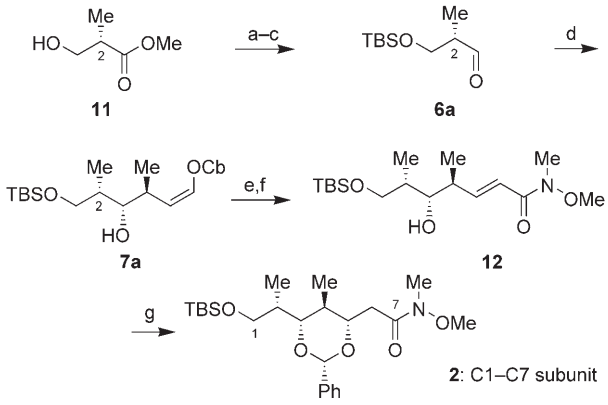
The synthesis of subunit **3** began with commercially available bromo alcohol **8** (Scheme 3). A reaction sequence involving cyanide displacement of the bromide, partial reduction of the resulting hydroxynitrile compound,[11] and direct dehydration provided the optically pure (*S*)-3-methyl-2,3-dihydrofuran (**9**) in 64% overall yield for three steps. The stereochemical control of the C13–C14 trisubstituted functionalized *Z* double bond was based on 1,2-cuprate transfer between the 5-lithio derivative of **9** and a cyano-Gilman dimethyl cuprate, $Me_2CuLi{\cdot}LiCN$. The use of various additives, and in particular those containing sulfur, allowed the efficient installation of a methyl group, which remained the most difficult to introduce.[12] After tri-*n*-butyltin chloride trapping, the unique *Z*-vinyltin derivative **10** was obtained in an optimized yield of 68%.



Scheme 3. Synthesis of the C8–C14 subunit **3**. a) NaCN, DMSO, 60°C, 24 h, 92%; b) DIBAL-H, CH_2Cl_2, −78°C, 2 h, 82%; c) *p*-TSA (0.2 mol%), quinoline, 160→210°C, 30 min, 85%; d) *t*BuLi, $Me_2CuLi_2{\cdot}LiCN$, Et_2O/DMS (4:1), 0°C→RT, 18 h, then nBu_3SnCl, −20°C→RT, 4 h, 68%; e) TEMPO (10 mol%), $PhI(OAc)_2$, CH_2Cl_2, RT, 2 h; f) **5**, pentane/cyclohexane, −78°C, 3 h, 84% (two steps); g) *t*BuLi, Et_2O, −40→−20°C, 20 min, 78%; h) MOMCl, TBAI, Hünig's base, CH_2Cl_2, 18 h, 92%. DIBAL-H = diisobutylaluminum hydride, *p*-TSA = *p*-toluenesulfonic acid, DMS = dimethyl sulfide, TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy free radical, MOM = methoxymethyl, TBAI = tetra-*n*-butylammonium iodide, Hünig's base = diisopropylethylamine.

A very large number of oxidation conditions were tested on alcohol **10**, but only the use of TEMPO/$PhI(OAc)_2$ led to the expected aldehyde **6b**.[13] Subsequent allylation of **6b** with the *R*-crotyltitanium **5** delivered the pure adduct **7b** in 84% yield for two steps (no other isomers were detected by NMR analysis). A Fritsch–Buttenberg–Wiechell rearrangement allowed the transformation of the *O*-enecarbamate **7b** into the terminal alkyne by treatment with *t*BuLi.[14] Notably, this α-elimination reaction, which used two equivalents of *t*BuLi, was faster than the tin/lithium exchange. Subunit **3** was obtained in 26.4% overall yield for eight steps.

To elaborate subunit **2**, the optically pure aldehyde **6a** was needed (Scheme 4). This compound could be obtained by classical chemistry in three steps from commercially available

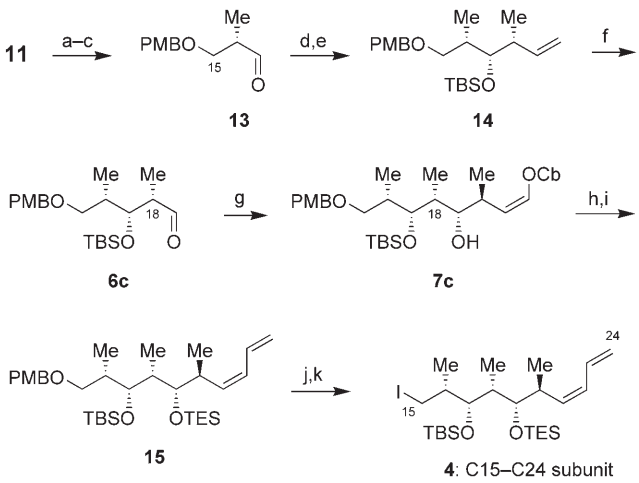


Scheme 4. Synthesis of the C1–C7 subunit **2**. a) TBSCl, imid, DMF, 0°C→RT, 18 h, 98%; b) DIBAL-H, CH_2Cl_2, −20°C, 30 min, 92%; c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −55°C→RT, 1 h; d) **5**, pentane/cyclohexane, −78°C, 3 h, 66% (two steps); e) O_3, sudan III, CH_2Cl_2, −78°C, 1 h then PPh_3, −78°C→RT, 3 h, 87%; f) $(EtO)_2P(O)CH_2C(O)$-NMe(OMe), NaH, THF, 0°C→RT, 45 min, 86%; g) PhCHO, KHMDS, THF, −20°C, 45 min, 79%. TBS = *tert*-butyldimethylsilyl, imid = imidazole, KHMDS = potassium bis(trimethylsilyl)amide.

(2*S*)-3-hydroxy-2-methylpropionic acid methyl ester (**11**; Roche ester).[15] The crotyltitanation reaction between aldehyde **6a** and *R*-crotyltitanium **5** furnished homoaldol compound **7a** in 66% yield for two steps with total diastereoselectivity. The *O*-enecarbamate function of **7a** has been deoxygenated under reducing conditions using isopropylmagnesium chloride and a nickel catalyst.[16] To our surprise, all attempts to transform this terminal alkene into an α,β-unsaturated Weinreb amide function by cross-metathesis reaction using Grubbs II or Hoveyda catalyst[17] failed, and only the starting material was recovered.[18] Therefore, we undertook an oxidation of *O*-enecarbamate **7a** with ozone; the resulting aldehyde was used in a Horner–Wadsworth–Emmons reaction with the commercially available diethyl (*N*-methoxy-*N*-methylcarbamoylmethyl)phosphonate to provide the expected α,β-unsaturated Weinreb amide **12** as a single stereomer. A hetero-Michael reaction, with benzaldehyde under anionic conditions, introduced the stereocenter in position C5 and simultaneously protected the C3 and C5 hydroxy functions as a benzylidene group (diastereomeric

ratio >95:5).[19] This sequence resulted in the effective formation of subunit **2**, in 35.2% overall yield for seven steps.

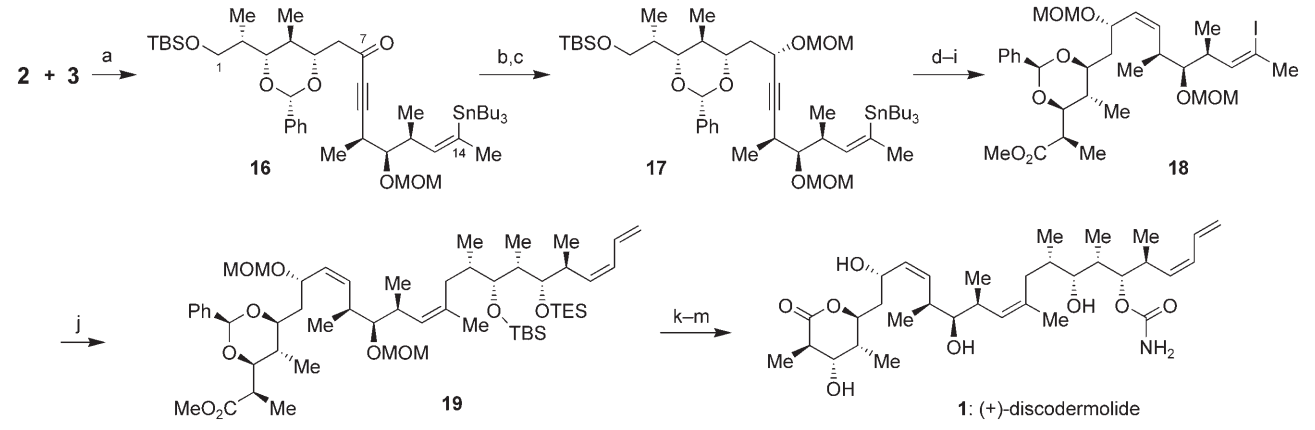
The same Roche ester **11** was used for the preparation of the third subunit **4** (Scheme 5). This starting material was transformed into aldehyde **13** by successive protection, reduction, and TEMPO/sodium chlorite oxidation.[20] The C16–C18 *syn–syn* stereotriad was installed by a $BF_3{\cdot}OEt_2$-catalyzed allylation reaction using achiral tri-*n*-butylcrotylstannane under simple asymmetric induction conditions (the diastereomeric ratio was optimized to 95:5).[21] Protection of the C17 hydroxy group allowed the isolation of the expected major isomer **14** (74% yield for two steps). An oxidative cleavage of this alkene then delivered the desired aldehyde **6c**.



Scheme 5. Synthesis of the C15–C24 subunit **4**. a) $CCl_3C(N)OPMB$, PPTS (5 mol%), CH_2Cl_2/cyclohexane, 20°C, 40 h, 88%; b) LAH, THF, 0°C→RT, 3 h, 95%; c) TEMPO (2 mol%), NaOCl, KBr, $NaHCO_3$, CH_2Cl_2/H_2O; d) tri-*n*-butylcrotylstannane, $BF_3{\cdot}OEt_2$, Et_2O, −100°C, 2 h, 74% (two steps); e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT, 2 h, 92%; f) O_3, sudan III, CH_2Cl_2/MeOH, −78°C, 2 h then Me_2S, −78°C→RT, 16 h; g) **5**, pentane/cyclohexane, −78°C, 3 h, 77% (two steps); h) TESOTf, 2,6-lutidine, CH_2Cl_2, 0°C→RT, 1.5 h, 78%; i) vinylmagnesium bromide, [Ni(acac)$_2$] (10 mol%), Et_2O, 0°C, 16 h, 85%; j) DDQ, CH_2Cl_2/H_2O, 0°C→RT, 40 min, 72%; k) I_2, PPh_3, imid, C_6H_6/Et_2O, 0°C→RT, 2 h, 79%. PMB = *p*-methoxybenzyl, PPTS = pyridinium *p*-toluenesulfonate, LAH = lithium aluminum hydride, Tf = trifluoromethanesulfonyl, TES = triethylsilyl, acac = acetylacetonate, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

In a single step, both the C18–C20 *syn–anti* stereotriad and the C21–C22 *Z* double bond were set up by an allylation reaction of **6c** with *R*-crotyltitanium **5**. Therefore, carbamate **7c** was elaborated in 77% yield and total selectivity from alkene **14**. Protection of the C19 hydroxy group and subsequent direct vinylation by a cross-coupling [Ni(acac)$_2$]-catalyzed reaction[22] between the *Z*-*O*-enecarbamate moiety and commercially available vinylmagnesium bromide furnished the *Z* diene **15** in 85% yield.[23] After regeneration of the C15 primary hydroxy group, the clean transformation into alkyl iodide **4** was realized under optimized Garegg conditions in a benzene/diethyl ether mixture under high dilution.[24] In this way, the final subunit **4** bearing five stereocenters and the terminal diene was obtained in 16.5% overall yield for 11 steps.

The first coupling reaction of the subunits was achieved by nucleophilic addition of an organometallic species derived from **3** on Weinreb amide **2** (Scheme 6). Reaction of **2** with the lithio derivative of **3**, generated by metalation with *t*BuLi, afforded the ynone **16** in 80% yield. Reduction of **16** with the CBS reagent allowed generation of the C7 stereocenter (diastereomeric ratio >95:5).[25] After protection of the C7 hydroxy group, regeneration of the primary alcohol at C1, and oxidation under TEMPO/$PhI(OAc)_2$ conditions, the crude aldehyde was treated with sodium chlorite[26] to afford a carboxylic acid, which was readily converted into its methyl ester with TMS-diazomethane.[27] The partial reduction of the triple bond at C8–C9 was realized with PtO_2.[28] Finally, iododestannylation gave the required vinyl iodide **18** in 30.6% overall yield for nine steps.



Scheme 6. Coupling reactions and total synthesis of (+)-discodermolide (**1**). a) **3**, *t*BuLi, Et_2O, −78°C, 30 min, then **2**, 0°C, 3 h, 80%; b) (*S*)-(−)-2-methyl-CBS-oxazaborolidine, $BH_3{\cdot}Me_2S$, THF, −30°C, 2 h, 95%; c) MOMCl, TBAI, Hünig's base, CH_2Cl_2, RT, 18 h, 86%; d) HF/py, py/THF, RT, 4 h, 96%; e) TEMPO (10 mol%), $PhI(OAc)_2$, CH_2Cl_2, RT, 3 h; f) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*BuOH/H_2O, RT, 1 h; g) TMS-CHN_2, C_6H_6/MeOH, RT, 15 min, 66% (three steps); h) H_2, PtO_2 (30 mol%), AcOEt, RT, 12 h; i) I_2, CH_2Cl_2, 0°C, 10 min, 71% (two steps); j) **4**, *t*BuLi, Et_2O, −78°C, 5 min, *B*-methoxy-9-BBN, THF, −78°C→RT, then **18**, $CsCO_3$, [Pd(dppf)Cl_2], $AsPh_3$, DMF, H_2O, 18 h, 60%; k) *p*-TSA, MeOH, 0°C, 1 h, 77%; l) $Cl_3CC(O)NCO$, CH_2Cl_2, RT, 15 min, then K_2CO_3, MeOH, RT, 1.5 h, 64%; m) HCl (4 N), THF, RT, 72 h, 70%. CBS = Corey–Bakshi–Shibata reagent, py = pyridine, TMS = trimethylsilyl, BBN = borabicyclo[3.3.1]nonane, dppf = (diphenylphosphino)ferrocene.

The σ bond between the major fragment **18** and subunit **4** was formed by a *B*-alkyl Suzuki–Miyaura cross-coupling reaction.[29] The reactive trialkyl boronate species, prepared from alkyl iodide **4** with *t*BuLi and *B*-methoxy-9-BBN, reacted with **18** under [Pd(dppf)Cl_2] and $AsPh_3$ conditions[30] to give the fully elaborated discodermolide carbon skeleton **19** in 60% yield.

After cleavage of the C19 triethylsilyl group and installation of the carbamate moiety,[31] the final global deprotection of all protecting groups, with concomitant lactonization, was performed in a 4 N HCl solution in THF. Purification of the crude product by flash chromatography (CH_2Cl_2/MeOH 80:20) afforded (+)-discodermolide (**1**) in 70% yield.

The spectroscopic data observed for our synthetic **1** (^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry) were identical in all respects with those reported for the natural material or another synthetic discodermolide. The specific optical rotation, $[\alpha]_D^{20} = +16.2\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.0\ \mathrm{g\,cm^{-3}}$, MeOH), was very close to previously reported values. In addition, in vitro cytotoxicity levels comparable to literature data[1,2] were obtained.

In conclusion, the total synthesis of discodermolide was achieved in 21 linear steps with 1.6% overall yield from commercially available compounds (**8** or **11**). We have shown homoallylic *Z*-*O*-enecarbamate alcohols to be powerful tools in the total synthesis of multifunctional compounds. Allylation reaction of α-(*S*)-methyl aldehydes **6a–c** with enantioenriched *R*-α-oxygenated crotyltitanium **5**, conveniently prepared in situ, ensured the stereocontrolled elaboration, for each subunit, of *syn–anti* methyl–hydroxy–methyl triads connected to a *Z*-*O*-enecarbamate. This particular group allowed direct and easy access to either a triple bond or terminal *Z* diene functions. This efficient and versatile synthesis delivered the natural product, and we are currently looking to extend this methodology to the preparation of original, unnatural discodermolide analogues.

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[1] a) S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1990**, *55*, 4912 – 4915; b) S. P. Gunasekera, M. Gunasekera, R. E. Longley, G. K. Schulte, *J. Org. Chem.* **1991**, *56*, 1346; c) S. P. Gunasekera, G. K. Paul, R. E. Longley, R. A. Isbruker, S. A. Pomponi, *J. Nat. Prod.* **2002**, *65*, 1643 – 1648.

[2] For major reports on biological studies, see: a) V. M. Sánchez-Pedregal, K. Kubicek, J. Meiler, I. Lyothier, I. Paterson, T. Carlomagno, *Angew. Chem.* **2006**, *118*, 7548 – 7554; *Angew. Chem. Int. Ed.* **2006**, *45*, 7388 – 7394; b) S. Xia, C. S. Kenesky, P. V. Rucker, A. B. Smith III, G. A. Orr, S. B. Horwitz, *Biochemistry* **2006**, *45*, 11762 – 11775; c) S. Honore, K. Kamath, D. Braguer, L. Wilson, C. Briand, M. A. Jordan, *Mol. Cancer Ther.* **2003**, *2*, 1303 – 1311; d) L. He, G. A. Orr, S. B. Horwitz, *Drug Discov. Today* **2001**, *6*, 1153 – 1164; e) L. He, H. Y. Chia-Ping, S. B. Horwitz, *Mol. Cancer Ther.* **2001**, *1*, 3 – 10; f) L. A. Martello, M. J. LaMarche, L. He, T. J. Beauchamp, A. B. Smith III, S. B. Horwitz, *Chem. Biol.* **2001**, *8*, 843 – 855; g) M. Kalesse, *ChemBioChem* **2000**, *1*, 171 – 175; h) E. ter Haar, R. J. Kowalski, E. Hamel, C. M. Lin, R. E. Longley, S. P. Gunasekera, H. S. Rosenkranz, B. W. Day, *Biochemistry* **1996**, *35*, 243 – 250; i) R. Balachandran, E. ter Haar, M. J. Welsh, S. G. Grant, B. W. Day, *Anticancer Drugs* **1998**, *9*, 67 – 76.

[3] a) G. S. Huang, L. Lopez-Barcons, B. S. Freeze, A. B. Smith III, G. L. Goldberg, S. B. Horwitz, H. M. McDaid, *Clin. Cancer Res.* **2006**, *12*, 298 – 304; b) L. A. Martello, H. M. McDaid, D. L. Regl, C.-P. H. Yang, D. Meng, T. R. R. Pettus, M. D. Kaufman, H. Arimoto, S. J. Danishefsky, A. B. Smith III, S. B. Horwitz, *Clin. Cancer Res.* **2000**, *6*, 1978 – 1987.

[4] For major publications on total synthesis, see: a) J. B. Nerenberg, D. T. Hung, P. K. Somers, S. L. Schreiber, *J. Am. Chem. Soc.* **1993**, *115*, 12621 – 12622; b) D. T. Hung, J. B. Nerenberg, S. L. Schreiber, *J. Am. Chem. Soc.* **1996**, *118*, 11054 – 11080; c) A. B. Smith III, Y. Qiu, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **1995**, *117*, 12011 – 12012; d) A. B. Smith III, T. J. Beauchamp, M. J. LaMarche, M. D. Kaufman, Y. Qiu, H. Arimoto, D. R. Jones, K. Kobayashi, *J. Am. Chem. Soc.* **2000**, *122*, 8654 – 8664, and references therein; e) S. S. Harried, G. Yang, M. A. Strawn, D. C. Myles, *J. Org. Chem.* **1997**, *62*, 6098 – 6099; f) S. S. Harried, C. P. Lee, G. Yang, T. I. H. Lee, D. C. Myles, *J. Org. Chem.* **2003**, *68*, 6646 – 6660; g) J. A. Marshall, Z.-H. Lu, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 817 – 823; h) J. A. Marshall, B. A. Johns, *J. Org. Chem.* **1998**, *63*, 7885 – 7892; i) I. Paterson, G. J. Florence, K. Gerlach, J. P. Scott, *Angew. Chem.* **2000**, *112*, 385 – 388; *Angew. Chem. Int. Ed.* **2000**, *39*, 377 – 380; j) I. Paterson, G. J. Florence, *Eur. J. Org. Chem.* **2003**, 2193 – 2208; k) I. Paterson, I. Lyothier, *J. Org. Chem.* **2005**, *70*, 5494 – 5507, and references therein; l) S. J. Mickel, D. Niederer, R. Daeffler, A. Osmani, E. Kuesters, E. Schmid, K. Schaer, R. Gamboni, W. Chen, E. Loeser, F. R. Kinder, Jr., K. Konigsberger, K. Prasad, T. M. Ramsey, O. Repič, R.-M. Wang, G. Florence, I. Lyothier, I. Paterson, *Org. Process Res. Dev.* **2004**, *8*, 122 – 130, and four precedent papers; m) S. J. Mickel, R. Daeffler, W. Prikoszovich, *Org. Process Res. Dev.* **2005**, *9*, 113 – 120; n) O. Loiseleur, G. Koch, J. Cercus, F. Schürch, *Org. Process Res. Dev.* **2005**, *9*, 259 – 271; o) A. Arefolov, J. S. Panek, *J. Am. Chem. Soc.* **2005**, *127*, 5596 – 5603, and references therein.

[5] a) D. Hoppe, *Angew. Chem.* **1984**, *96*, 930 – 946; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 932 – 948; b) D. Hoppe, O. Zschage, *Angew. Chem.* **1989**, *101*, 67 – 69; *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 69 – 71; c) D. Hoppe, O. Zschage, *Tetrahedron* **1992**, *48*, 8389 – 8392.

[6] a) V. Fargeas, P. Le Ménez, I. Berque, J. Ardisson, A. Pancrazi, *Tetrahedron* **1996**, *52*, 6613 – 6634; b) I. Berque, P. Le Ménez, P. Razon, C. Anies, A. Pancrazi, J. Ardisson, A. Neuman, T. Prangé, J.-D. Brion, *Synlett* **1998**, 1132 – 1134; c) I. Berque, P. Le Ménez, P. Razon, A. Pancrazi, J. Ardisson, J.-D. Brion, *Synlett* **1998**, 1135 – 1137; d) I. Berque, P. Le Ménez, P. Razon, J. Mahuteau, J.-P. Férézou, A. Pancrazi, J. Ardisson, J.-D. Brion, *J. Org. Chem.* **1999**, *64*, 373 – 381.

[7] D. Hoppe, T. Hense, *Angew. Chem.* **1997**, *109*, 2376 – 2410; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2282 – 2316.

[8] T. Fujisawa, Y. Kurita, M. Kawashima, T. Sato, *Chem. Lett.* **1982**, 1641 – 1642.

[9] a) P. Kocienski, S. Wadman, K. Cooper, *J. Am. Chem. Soc.* **1989**, *111*, 2363 – 2365; b) P. Kocienski, C. Barber, *Pure Appl. Chem.* **1990**, *62*, 1933 – 1940.

[10] a) P. Le Ménez, V. Fargeas, I. Berque, J. Poisson, J. Ardisson, J.-Y. Lallemand, A. Pancrazi, *J. Org. Chem.* **1995**, *60*, 3592 – 3599; b) V. Fargeas, P. Le Ménez, I. Berque, J. Ardisson, A. Pancrazi, *Tetrahedron* **1996**, *52*, 6613 – 6634.

[11] M. A. Evans, J. P. Morken, *Org. Lett.* **2005**, *7*, 3371 – 3373.

[12] a) E. de Lemos, F.-H. Porée, J.-F. Betzer, A. Pancrazi, J. Ardisson, unpublished results; b) K. Jarowicki, P. Kocienski, S.

Norris, M. O'Shea, M. Stocks, *Synthesis* **1995**, 195 – 198; c) P. Ashworth, B. Broadbelt, P. Jankowski, P. Kocienski, A. Pimm, R. Bell, *Synthesis* **1995**, 199 – 206; d) A. Pommier, V. Stepanenko, K. Jarowicki, P. J. Kocienski, *J. Org. Chem.* **2003**, *68*, 4008 – 4013.
[13] A. De Mico, R. Margarita, L. Parlanti, A. Vescovi, G. Piancatelli, *J. Org. Chem.* **1997**, *62*, 6974 – 6977.
[14] a) P. Fritsch, *Justus Liebigs Ann. Chem.* **1894**, *279*, 319 – 323; b) W. P. Buttenberg, *Justus Liebigs Ann. Chem.* **1894**, *279*, 324 – 337; c) H. Wiechell, *Justus Liebigs Ann. Chem.* **1894**, *279*, 337 – 344; For reviews, see: d) M. Braun, *Angew. Chem.* **1998**, *110*, 444 – 465; *Angew. Chem. Int. Ed.* **1998**, *37*, 430 – 451; e) R. Knorr, *Chem. Rev.* **2004**, *104*, 3795 – 3849.
[15] W. R. Roush, A. D. Palkowitz, K. Ando, *J. Am. Chem. Soc.* **1990**, *112*, 6348 – 6359.
[16] a) P. Kocienski, N. J. Dixon, *Synlett* **1989**, 52 – 54; b) R. W. Hoffmann, V. Giesen, M. Fuest, *Liebigs Ann. Chem.* **1993**, 629 – 639.
[17] a) A. Fürstner, *Angew. Chem.* **2000**, *112*, 3140 – 3172; *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 – 3043; b) J. Cossy, S. BouzBouz, A. H. Hoveyda, *J. Organomet. Chem.* **2001**, *634*, 216 – 221; c) T.-L. Choi, A. K. Chatterjee, R. H. Grubbs, *Angew. Chem.* **2001**, *113*, 1317 – 1319; *Angew. Chem. Int. Ed.* **2001**, *40*, 1277 – 1279.
[18] Direct attempts carried out on compound **7a** failed.
[19] J. A. Gauchet-Prunet, D. A. Evans, *J. Org. Chem.* **1993**, *58*, 2446 – 2453.
[20] P. L. Anelli, C. Biffi, F. Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559 – 2562.
[21] a) G. E. Keck, D. E. Abbott, *Tetrahedron Lett.* **1984**, *25*, 1883 – 1886; b) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama, *Tetrahedron* **1984**, *40*, 2239 – 2246; c) G. E. Keck, K. A. Savin, N. K. Cressman, D. E. Abbott, *J. Org. Chem.* **1994**, *59*, 7889 – 7896.
[22] a) E. Wenkert, E. L. Michelotti, C. S. Swindell, *J. Am. Chem. Soc.* **1979**, *101*, 2246 – 2247; b) E. Wenkert, E. L. Michelotti, C. S. Swindell, M. Tingoli, *J. Org. Chem.* **1984**, *49*, 4894 – 4899.
[23] F.-H. Porée, A. Clavel, J.-F. Betzer, A. Pancrazi, J. Ardisson, *Tetrahedron Lett.* **2003**, *44*, 7553 – 7556.
[24] a) P. J. Garegg, B. Samuelsson, *J. Chem. Soc. Perkin Trans. 1* **1980**, 2866 – 2869; b) E. J. Corey, S. G. Pyne, W.-G. Su, *Tetrahedron Lett.* **1983**, *24*, 4883 – 4886.
[25] a) E. J. Corey, R. K. Bakshi, S. Shibata, *J. Am. Chem. Soc.* **1987**, *109*, 5551 – 5553; b) E. J. Corey, C. J. Helal, *Angew. Chem.* **1998**, *110*, 2092 – 2118; *Angew. Chem. Int. Ed.* **1998**, *37*, 1986 – 2012.
[26] E. Dalcanale, F. Montanari, *J. Org. Chem.* **1986**, *51*, 567 – 569.
[27] a) N. Hashimoto, T. Aoyama, T. Shioiri, *Chem. Pharm. Bull.* **1981**, *29*, 1475 – 1478; b) Y. Hirai, T. Aida, S. Inoue, *J. Am. Chem. Soc.* **1989**, *111*, 3062 – 3063.
[28] L. F. Tietze, J. Görlitzer, A. Schuffenhauer, M. Hübner, *Eur. J. Org. Chem.* **1999**, 1075 – 1084.
[29] S. R. Chemler, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4676 – 4701; *Angew. Chem. Int. Ed.* **2001**, *40*, 4544 – 4568.
[30] J. A. Marshall, G. M. Schaaf, *J. Org. Chem.* **2003**, *68*, 7428 – 7432.
[31] P. Kočovský, *Tetrahedron Lett.* **1986**, *27*, 5521 – 5524.

