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Studies on the Synthesis of the ABC Rings of (±)-Hexacyclinic Acid†

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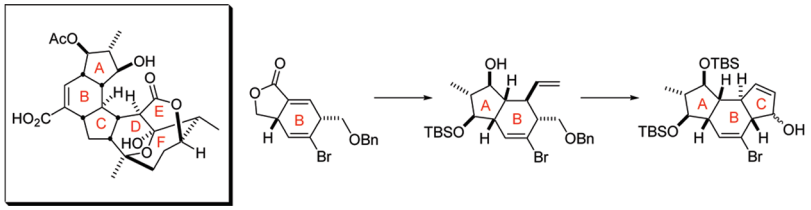

A synthesis of the ABC-rings of the polyketide natural product hexacyclinic acid has been achieved. The B-ring was formed first via an intramolecular ester-tethered Diels−Alder reaction, and the A-ring was annulated to this by means of a SmI_2 mediated reductive 5-*exo-trig* cyclization of a samarium−ketyl radical onto a vinyl group. Finally, the C-ring was closed using olefin metathesis. Interestingly, use of enyne metathesis resulted in the synthesis of a more functionalized 5-membered C-ring in a model system, but an undesired 6-membered C-ring in the actual system. An investigation of this change in selectivity is discussed.

Introduction

Hexacyclinic acid was isolated from a strain of *Streptomyces* using the OSMAC (one strain/many compounds approach) (Figure 1). After extensive optimization, 56 mg L^{-1} of a new metabolite was isolated from the organic extracts after column chromatography using $CHCl_3$/methanol as the mobile phase. Extensive spectroscopic studies indicated that the structure of this new metabolite was hexacyclinic acid; this was subsequently confirmed by X-ray single-crystal analysis.[1] The absolute stereochemistry of hexacyclinic acid was determined by performing advanced Mosher's ester methodology on the C16 (X-ray numbering) hydroxyl on the A-ring. The polyketide nature of hexacyclinic acid was confirmed by ^{13}C-labeled feeding experiments. This showed that seven acetate and four propionate units made up the carbon skeleton of hexacyclinic acid;[1] however, a definitive biosynthetic pathway was not elucidated. When tested in three cell lines (HM02, HEPG2 and MCF7), hexacyclinic acid showed some cytotoxicity with GI_{50} values in the low μM range;[1] further biological results have yet to be reported. While this cytotoxicity is lower than that of the related compound FR182877,[2] since no structure−activity studies have been reported that compare hexacyclinic acid and FR182877, it is not known which features of FR182877 give it its increased cytotoxicity over hexacyclinic acid.

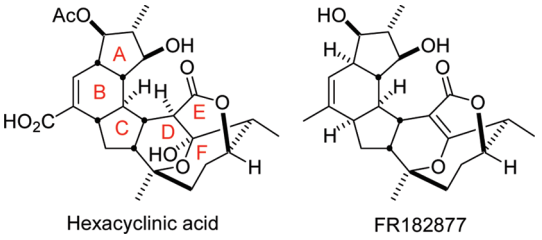

FIGURE 1. Structure of hexacyclinic acid and FR182877.

† Dedicated to Prof. Richard J. K. Taylor on the occasion of his 60th birthday.

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(1) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3258.

(2) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Takase, S.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Sato, B.; Nakajima, H.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204. (c) Yoshimura, S.; Sato, B.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.

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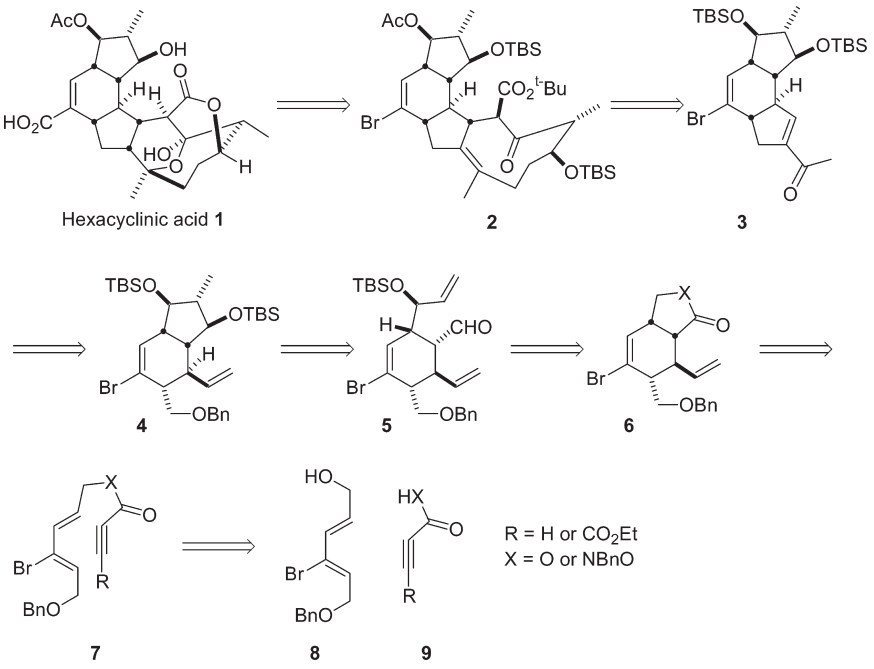
SCHEME 1. Retrosynthetic Analysis



While the related compound FR182877 has succumbed to total synthesis by the groups of Sorensen,[3] Evans,[4] and Nakada[5] and has been the subject of further synthetic activity,[6] hexacyclinic acid has not. To date, only four groups have published strategies toward fragments of hexacyclinic acid. The group of Landais has published a free-radical-mediated 5-*exo*-*trig* cyclization to yield a structure which has similarities to the ABC-rings of hexacyclinic acid.[7] The group of Kalesse has published a route to the ABC-rings of hexacyclinic acid which lack only the B-ring carboxylic acid function,[8] and the group of Prunet has published a ring-closing metathesis approach to the A-ring of hexacyclinic acid[9] and a Michael addition/radical cyclization approach to the functionalized ABC-rings of hexacyclinic acid.[10] Our own endeavors have resulted in the synthesis of the DEF-rings of both hexacyclinic acid and FR182877 by means of a transannular iodocyclisation reaction[11] and the synthesis of the AB-rings of hexacyclinic acid and the B-ring of FR182877 via an ester-tethered Diels−Alder approach.[12] In this paper, we disclose fully our studies toward and the synthesis of the ABC-rings of hexacyclinic acid.

Results and Discussion

Our retrosynthetic strategy is outlined in Scheme 1. Disconnection of the lactone and hemiketal units in hexacyclinic acid **1** provides a functionalized 9-membered ring **2**, which has the potential to cyclize in a transannular fashion to furnish the DEF-rings of the natural product.[11] Retrosynthetic removal of six of the carbons in the 9-membered ring reveals tricyclic ketone **3** as an ABC-ring subunit target. Disconnection of the C-ring reveals a functionalized AB-ring unit **4**, the A-ring of which was envisaged to be formed by means of a reductive 5-*exo*-*trig* cyclization of a ketyl radical onto a double bond **5**. The cyclcohexene ring **6** could then be disconnected back to a simple tethered diene/dienophile **7**. As we wished to keep our options open, we considered the use of either an alkenic or alkynic dienophile partner tethered to the diene by means of either an ester or hydroxamate linkage **7**. This in turn could be disconnected back to readily available simple Diels−Alder precursors **8**[13] and **9**.

Regardless of the dienophile, bromodiene **8** was required, and this was initially prepared from (*E*)-3-hydroxyprop-1-enylboronic acid and 3-(benzyloxy)-1,1-dibromoprop-1-ene in 77% yield.[12] However, the poor yields for the synthesis of (*E*)-3-hydroxyprop-1-enylboronic acid ($<25\%$) forced us to resort to a longer route which could ultimately service us with more material (an overall yield of 51% from *cis*-butene-1,4-diol).[13] With quantities of **8** in hand, we could now investigate the tethered Diels−Alder reaction. As previous studies with ester-tethered fumarates had shown that *exo*- vs *endo*-selectivity and competing sigmatropic rearrangements were a significant problem,[14] we decided to investigate the use of a hydroxamate tether as expounded by Ishikawa.[15]

(3) Vosburg, D. A; Vanderwal, C. D; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552.
(4) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787.
(5) Tanaka, N.; Suzuki, T.; Matsumura, T.; Hosoya, Y.; Nakada, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2580.
(6) (a) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585. (b) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223. (c) Funel, J.-A.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555.
(7) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985.
(8) (a) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889. (b) Stelmakh, A.; Stellfeld, T.; Kalesse, M. *Org. Lett.* **2006**, *8*, 3485.
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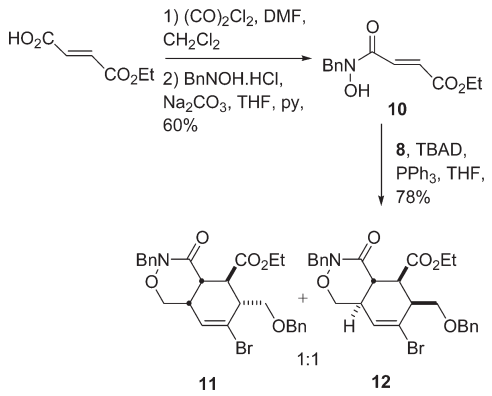
(11) (a) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560. (b) Clarke, P. A.; Grist, M.; Ebden, M. *Tetrahedron Lett.* **2004**, *45*, 927. (c) Clarke, P. A.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, *61*, 353.
(12) Clarke, P. A.; Cridland, A. P. *Org. Lett.* **2005**, *7*, 4221.
(13) Clarke, P. A.; Rolla, G. A.; Cridland, A. P.; Gill, A. A. *Tetrahedron* **2007**, *63*, 9124.
(14) Clarke, P. A.; Davie, R. L.; Peace, S. *Tetrahedron* **2005**, *61*, 2335.
(15) Ishikawa, T.; Senzaki, M.; Kadoya, R.; Marimoto, T.; Miyake, M.; Izawa, M.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 4607.

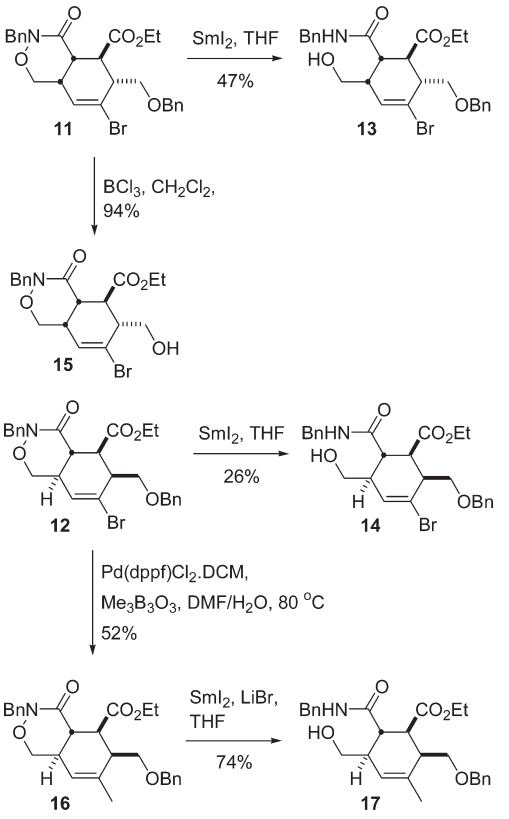
SCHEME 2. Hydroxamate-Tethered Diels–Alder Reaction



They showed that by the use of *N*-benzyl hydroxamate tethers the diastereoselectivity of the Diels–Alder reaction could be controlled to give exclusively the *endo*-Diels–Alder adduct, which is required for the synthesis of the B-ring of **1**.

Monoethyl fumarate was treated with oxalyl chloride in CH_2Cl_2 with catalytic DMF to generate the acid chloride which was then reacted with *N*-benzyl hydroxylamine to generate **10** in an unoptimized 60% yield. An attempt was made to form the tethered Diels–Alder precursor via a Mitsunobu coupling of **8** and **10**; however, cyclization proved too facile under these conditions and a 1:1 mixture of *exo*- and *endo*-Diels–Alder adducts were isolated in a combined yield of 78% (Scheme 2). While this was not what was expected, it was decided to use this opportunity to attempt the synthesis of the ABC-rings of both hexacyclinic acid and FR182877, as **11** had the correct configuration for hexacyclinic acid and **12** had the correct configuration for FR182877, and they could both be separated by flash column chromatography. Manipulation of **11** and **12** in an effort to form the A-ring was initially investigated (Scheme 3). This was attempted by reductive cleavage of the hydroxamate N–O bond by several methods such as $Zn/Cu(OAc)_2$ in $AcOH/H_2O$, SmI_2 in THF/H_2O, and Fe/HCl; however, they all failed to return anything other than starting material. Reagents such as $SnCl_2$/HCl, Zn/AcOH, and SmI_2 with HMPA/H_2O caused decomposition of the material. The only conditions to return an isolable product of N–O cleavage were SmI_2 in THF, which gave **13** and **14** in 47% and 26% yields, respectively. It was suspected that the problems with the reductive N–O cleavage could be traced to the vinyl bromide present in both **11** and **12**, and indeed when this was replaced in **12** with a methyl group **16**, as required for the synthesis of FR182877, the reduction went smoothly generating the desired N–O cleaved product in 74% yield. Reduction of the ethyl ester present in **11**, **13**, **16**, and **17** was investigated in order to install the required vinyl group of **6**. A number of methods including Dibal-H, $LiAlH_4$, and $LiBH_4$ were tried, but in no cases was any of the desired alcohol or aldehyde product formed. Oxidation of the alcohols in **13** and **17** was also attempted by Dess–Martin, Swern, PDC, SO_3·py/Hunig's base, MnO_2, and Pfitzer–Moffat conditions, but in all cases degradation resulted or the starting material was reisolated. The only modification which could be carried out successfully was removal of the

SCHEME 3. Manipulation of the Hydroxamate-Tethered Diels–Alder Adducts

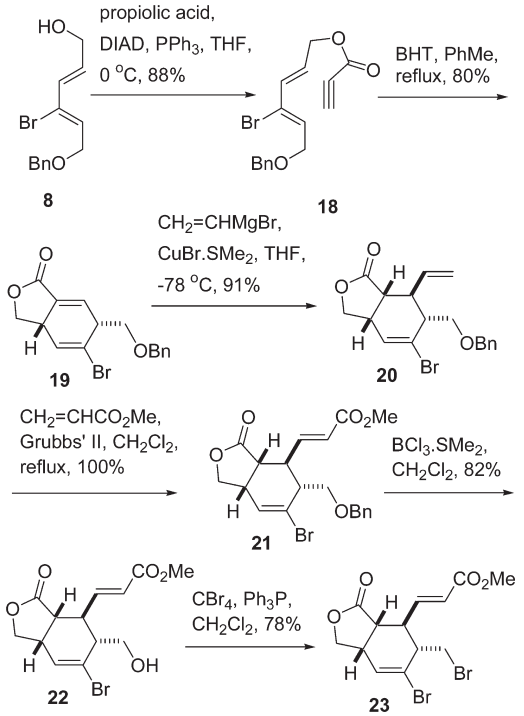


benzyl protecting group of **11** with BCl_3 to yield **15** in 94% yield.

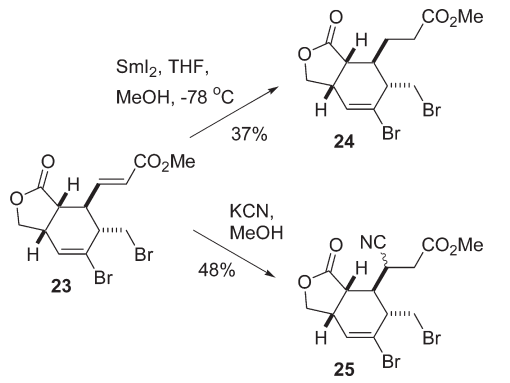
As ester-tethered fumarates had also proved problematic,[14] the decision was taken to examine the use of propiolates as the dienophile in the Diels–Alder cyclization, as the desired vinyl group functionality (e.g., **6**) could then be added via conjugate addition in a later step (Scheme 4). To this end, propiolic acid was joined to **8** under Mitsunobu conditions to give **18** in 88% yield and thermally cyclized in toluene under reflux to provide Diels–Alder adduct **19** in 80% yield. The vinyl group was introduced by a copper-catalyzed addition of vinyl Grignard, and this proceeded to give **20** in a 91% yield. The highly diastereoselective formation of the two new stereocenters is rationalized due to conjugate addition and subsequent enolate protonation, both occurring on the less hindered convex β-face of the molecule. A cross-metathesis with methyl acrylate using Grubbs II catalyst generated **21** in 100% yield. Removal of the benzyl group with $BCl_3 \cdot SMe_2$ complex proceeded in 82% yield and gave **22**, which was converted into **23** by the action of Ph_3P and CBr_4 in 78% yield.

With **23** in hand, it was now possible to explore the formation of the C-ring of hexacyclinic acid (Scheme 5). It was initially envisaged that the reduction of the α,β-unsaturated ester with SmI_2 would generate an enolate which could be alkylated intramolecularly by the pendant alkyl bromide to form the C-ring. While precedence for the cyclization of an enolate, generated in this way, onto an alkyl bromide was not found, it had been reported by Procter that enolates of α,β-unsaturated esters generated by the action of SmI_2 could be cyclized onto a pendant ketone

SCHEME 4. Propiolate-Tethered Formation of the B-Ring of Hexacyclinic Acid



SCHEME 5. Attempts at C-Ring Formation



carbonyl to form cyclopentanols in high yields.[16] However, use of the conditions reported by Procter resulted in the isolation of the saturated ester **24**, with none of the cyclized product being detected.

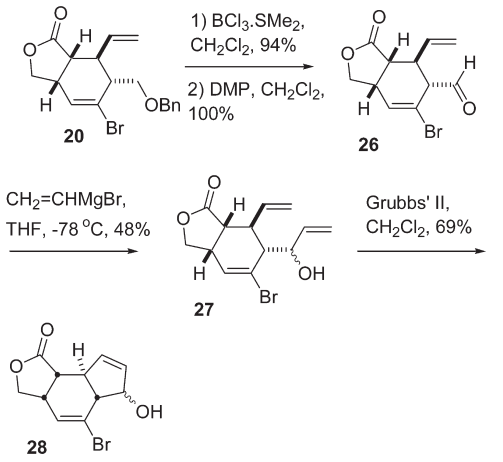
A report by Little showed that a cyclopentane ring could be formed by the cyclization of the enolate of an ester, formed by the conjugate addition of cyanide anion to an α,β-unsaturated ester, on to a primary alkyl bromide.[17] However, application of these conditions to **23** resulted in the product of simple conjugate addition being isolated as a mixture of diastereomers **25**.

With these methods failing to secure the formation of the C-ring it was decided to investigate the use of ring closing

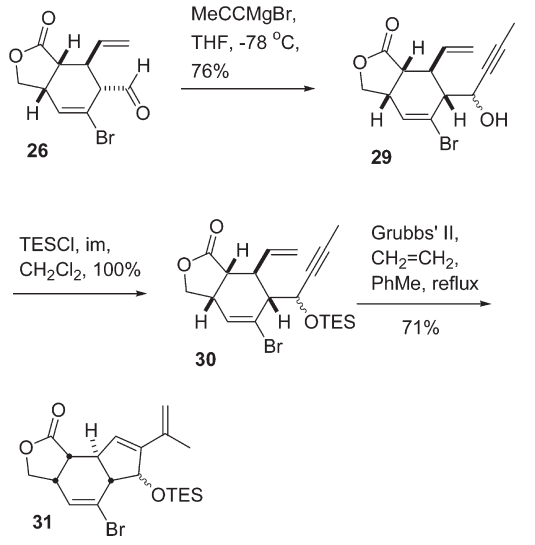
(16) (a) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2002**, *4*, 2345. (b) Hutton, T. K.; Muir, K.; Procter, D. J. *Org. Lett.* **2003**, *5*, 4811.

(17) Little, R. D.; Verhé, R.; Monte, W. T.; Nugent, S.; Dawson, R. J. *J. Org. Chem.* **1982**, *47*, 362.

SCHEME 6. Formation of the C-Ring via Ring-Closing Metathesis



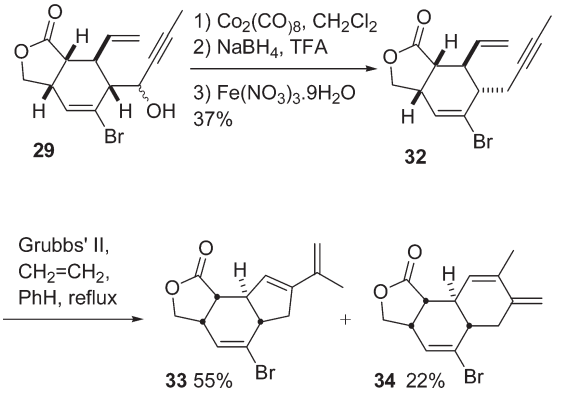
SCHEME 7. Formation of the C-Ring by Enyne Ring-Closing Metathesis



metathesis to form the C-ring (Scheme 6). To this end, the benzyl group of **20** was removed using $BCl_3 \cdot SMe_2$ complex and the resulting alcohol oxidized with Dess−Martin periodinane to aldehyde **26**. Interestingly, there was no sign of migration of the double bond into conjugation with the carbonyl group under these conditions. Aldehyde **26** was reacted with vinylmagnesium bromide to generate **27** as a mixture of diastereomeric alcohols, which in turn were cyclized to **28** in 69% yield by ring-closing metathesis using Grubbs' II catalyst. The mixture of diastereomers was inconsequential at this stage as the hydroxyl group would need to be removed for the completion of the synthesis of **1**.

However, at this time it was felt that there was insufficient functionality on the cyclopentenol C-ring in **28** to allow for easy elaboration of the DEF-rings, and so an alternative enyne metathesis was investigated (Scheme 7). Aldehyde **26** was treated with propynylmagnesium bromide to generate propargylic alcohol **29** as a 2.5: 1 mixture of diastereomers in 76% yield, which was then protected with TESCl and

SCHEME 8. Removal of the Hydroxyl and Formation of the C-Ring

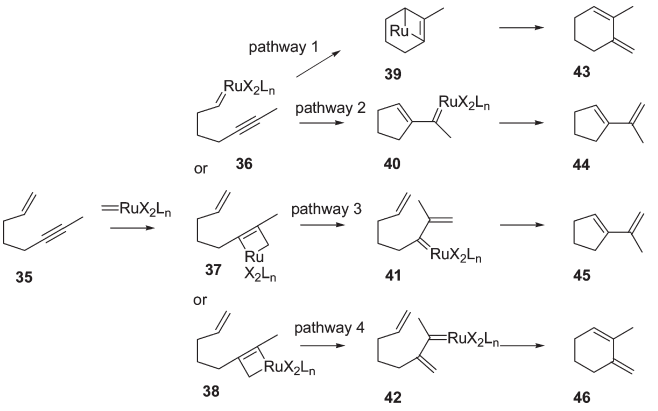


imidazole to give silyl ether **30** quantitatively. Enyne metathesis of **30** went smoothly in toluene under reflux with Grubbs' II catalyst to yield the BC-ring system **31** in 93% yield.

As the C-ring in hexacyclinic acid **1** does not possess a secondary hydroxyl group, the formation of a C-ring devoid of this functionality was attempted. It was decided not to investigate the removal of the hydroxyl group from **31** as it was anticipated that both ionic and radical-mediated removal could interfere with the double bonds and either promote reduction of one or both of them or even migration of the endocyclic double bond around the C-ring. Instead removal of the hydroxyl from propargylic alcohol **29** was investigated by use of a Nicholas reaction (Scheme 8). The acetylene of **29** was complexed with $Co_2(CO)_8$ and then treated with TFA to form the stabilized cation and then with $NaBH_4$ to reduce it to the methylene group. The $Co_2(CO)_6$ was then decomplexed by oxidation with $Fe(NO_3)_3 \cdot 9H_2O$ to give **32** in 37% yield. The use of $BF_3 \cdot OEt_2$ and Et_3SiH were also investigated in various combinations for the reduction step, as well as other methods for oxidative decomplexation such as NMO, $(NH_4)_2Ce(NO_3)_6$ and even O_2. Ultimately, however, the initial conditions proved to be the best. Although far from satisfactory, this route did provide some material to study the enyne metathesis reaction. Enyne metathesis of **32** with Grubbs' II catalyst generated two products in a 3:1 ratio which were identified as **33** and **34** respectively. It was surprising and disappointing that constitutional isomer **34** was now being formed under the reaction conditions.

The formation of **33** arises from one of two possible reaction pathways (Scheme 9): Pathway 2: the vinyl group reacts first with the catalyst to give **36** followed by the alkyne **40** in the so-called "ene-then-yne" mechanism. Alternatively, pathway 3: the alkyne reacts preferentially with the catalyst in a regioselective fashion, placing the ruthenium center closest to the 6-membered B-ring **41** before reacting with the vinyl group **45**. The formation of **34** can also arise from two different reaction pathways. In pathway 1, the vinyl group in reacts first with the catalyst **36** followed by the alkyne to give a highly strained metallocycle intermediate **39**, and for this reason this pathway was discounted.[18] More likely, in pathway 4, the alkyne reacts preferentially with the

SCHEME 9. Possible Mechanistic Pathways for the Formation of the Metathesis Products



catalyst in a regioselective fashion, placing the ruthenium center closest to the methyl group **38**, before then reacting with the vinyl group **46**.

It is possible that the single product **31** which arises from the reaction of **30** does so as the steric bulk of the silyl ether forces the catalyst to react via the "ene-then-yne" pathway 2. When the silyl ether is no longer present, **32** then the "yne-then-ene" pathways can also compete which leads to the formation of **34** as well as **33**. An alternative explanation may be that the catalyst can coordinate to the silyl ether oxygen[19] in **30**, which leads to regioselective formation of the alkyne addition intermediate **37** where the metal center is closest to the silyl ether, which would give rise to **31**. With the silyl ether removed **32**, addition of the catalyst to the alkyne in an uncontrolled fashion occurs giving rise to both products **33** and **34**.

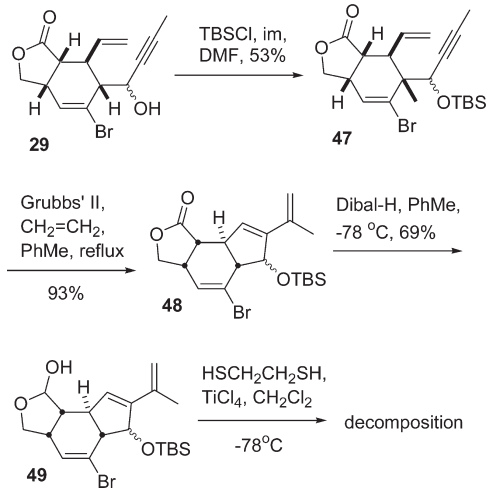
Due to the low-yielding removal of the hydroxyl group in the Nicholas reaction and the mixture of enyne metathesis products arising from the cyclization of **32**, it was instead decided to investigate formation of the A-ring from silyl ether **31** (Scheme 10). This was to be achieved via reduction of the lactone and opening of the resulting lactol with 1,2-ethanedithiol in order to form the dithiolane. However, the TES ether proved to be very labile under the reaction conditions, and so the more robust TBS ether **48** was employed. In this route, the lactone reduction yielded the lactol **49** in good yield, but opening of the lactol with 1,2-ethanedithiol and $TiCl_4$ only caused decomposition of **49**. As the initial B-ring to BC-ring to ABC-ring strategy had failed it was decided to investigate an alternative B-ring to AB-ring to ABC-ring route, which it was hoped would result in greater success.

Investigation of the B- to AB- to ABC-ring strategy began from lactone **20** (Scheme 11). Reduction of lactone **20** with Dibal-H proceeded smoothly to give **50** as a single diastereomer, the stereochemistry of the lactol stereogenic center was determined by X-ray crystallography, which also confirmed the stereochemical assignment around the cyclohexene ring (see Figure 1 in the Supporting Information). The lactol **50** was opened to form dithiolane **51** by the action of 1,2-ethanedithiol and $TiCl_4$. If the reaction was worked up

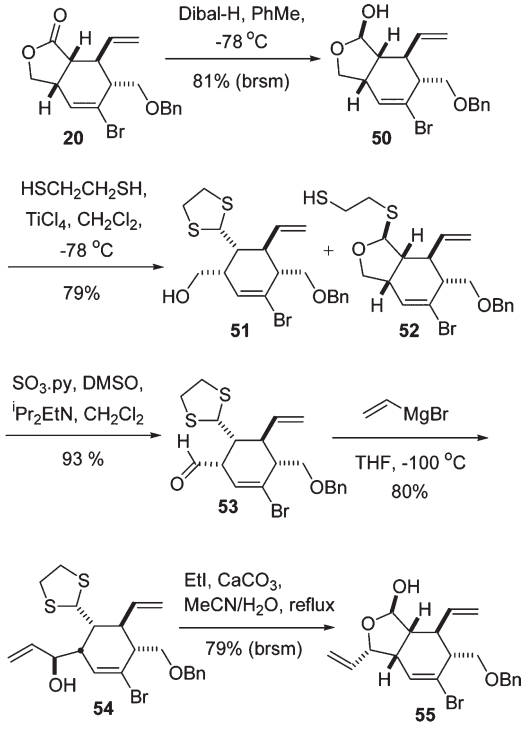
(18) Sashuk, V.; Grela, K. *J. Mol. Catal. A Chem.* **2006**, *257*, 59.

(19) For co-ordination to a hydroxyl group directing enyne metathesis, see: Niethe A.; Fischer, D.; Blechert, S. *J. Org. Chem.*, **2008**, *73*, 3088.

SCHEME 10. Investigation of A-Ring Formation from BC-Ring 48



SCHEME 11. En Route to the AB-Rings



too soon, hemithioacetal **52** could also be isolated; however, resubmission of this to the reaction conditions ensured its conversion into **51**. Oxidation with SO_3·py complex gave aldehyde **53**; interestingly, these were the only conditions that did not promote isomerization of the double bond into conjugation with the aldehyde carbonyl. The stage was now set for the introduction of the vinyl group required for reductive closure of the A-ring. It was rationalized, using a Felkin−Anh analysis, that treatment of aldehyde **53** with vinylmagnesium bromide would furnish a product where the major diastereomer was the one required for the continuation of the synthesis **54** (Figure 2). Indeed when **53** was treated with vinylmagnesium bromide at −100 °C, allylic

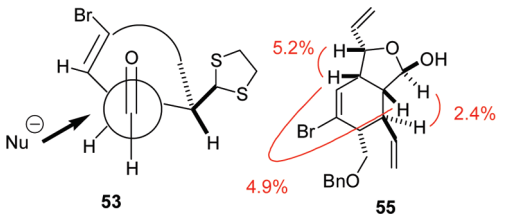
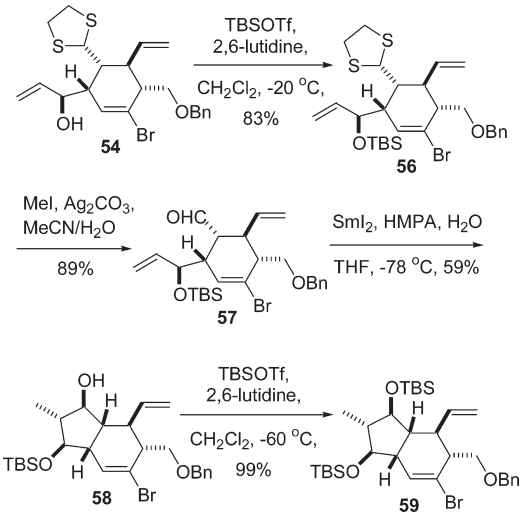


FIGURE 2. Felkin−Anh rationalization for the formation of **54** and diagnostic NOE data for lactol **55**.

SCHEME 12. Formation of the AB-Rings 59



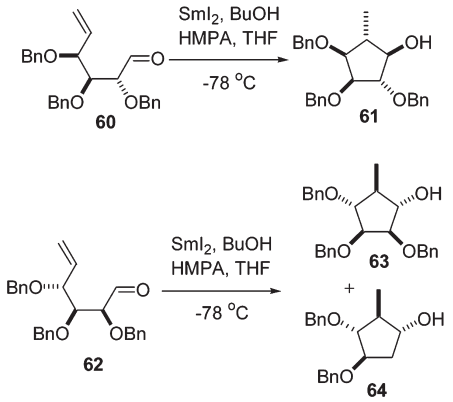
alcohol **54** was formed as the major product in a ratio of 30:1 and in an isolated yield of 80%.

Proof of the configuration of the newly formed stereogenic center was obtained by removing the dithiolane protecting group with EtI and $CaCO_3$ in $MeCN/H_2O$ under reflux and allowing lactol formation (Scheme 11). This generated lactol **55**, where the relative configurations of the stereogenic centers was determined by diagnostic NOE data (Figure 2).

With the stereochemistry of the vinyl addition confirmed as correct it was now possible to continue with the synthesis (Scheme 12). Allylic alcohol **54** was protected as the TBS ether **56** to avoid lactone formation upon removal of the dithiolane. Removal of the ditholane from **56** proved problematic at first. The conditions employed previously for the deprotection of **54** had provided enough material for diagnostic purposes only and were unsuitable for a multistep synthesis and so were not initially investigated in the removal of the dithiolane from **56**. Alternative reagents like $HgCl_2$ and $NCS/AgNO_3$ left the dithiolane unit intact. Oxidizing agents have been reported to remove dithiolanes; however, use of either DMP,[20] IBX, or CAN[21] resulted in decomposition as did $Tl(NO_3)_3$. Use of bis(trifluoroacetoxy)iodobenzene[22] did furnish some of the desired aldehyde **57**, but in less than 20% yield. With this lack of success it was decided to return to examine the original deprotection conditions. Reaction was slow with EtI and $CaCO_3$ in $MeCN/H_2O$, and

(20) Langille, N. F.; Dakin, L. A.; Panek, J. S. *Org. Lett.* **2003**, *5*, 575.
(21) Ho, T.-L.; Ho, H. C.; Wong, C. M. *J. Chem. Soc., Chem. Commun.* **1972**, 791.
(22) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 287.

SCHEME 13. Holzapfel's SmI_2-Promoted Cyclizations to Cyclopentanols



while warming increased the rate of the reaction, it also led to some decomposition of the material. This necessitated purification via flash column chromatography, which was undesirable as the aldehyde **57** was prone to decomposition on silica gel. Changing EtI for MeI did speed the reaction slightly,[23] but 24 h was still excessive. As heating caused decomposition it was necessary to find other ways to increase the rate of reaction and the role of the base was next investigated. It was decided to employ a base with a greater affinity for iodine and the use of Tl_2CO_3 meant the reaction was over in 3 days and **57** could be isolated in 62% yield with no need for purification. However, the breakthrough came with the use of Ag_2CO_3, which increased the rate of the reaction to such an extent that it was over in 24 h and aldehyde **57** could be isolated in 93% yield without the need for purification.

With aldehyde **57** in hand, the key reductive A-ring annulation reaction could be investigated. The first conditions tried were those reported by Holzapfel[24] (SmI_2, HMPA, BuOH in THF at −78 °C) for the cyclization of **60** to **61** and **62** to **63** (Scheme 13) which showed that the desired *anti-anti* stereochemistry between the already present benzyl ether functionality and the newly formed methyl group and the newly formed alcohol could be obtained. It is this relative stereochemistry which is required for the synthesis of the A-ring of **1**. However, when **57** was subjected to these reaction conditions the major product **58** was isolated from the reaction but only in a 23% yield. The structure and stereochemistry of **58** were determined by 2D NMR experiments and NOE interactions (Figure 3).

As **58** was only formed in 23% yield an improvement was sought. Attempts to remove the use of HMPA resorted in the formation of alcohol **65** with no product of cyclization seen[25] (Figure 4). When *n*-BuOH was replaced with bulky non-coordinating *t*-BuOH,[26] **58** was again formed in 23% yield but dimer **66** was also isolated in 43% yield (Figure 4). As **57** was racemic, **66** was formed as a mixture of *meso*- and *d*/*l*-isomers, and while they were separable individual assignment was not possible. Mechanistically, the dimers **66** form

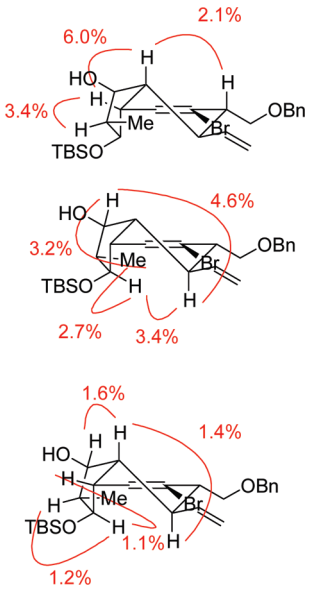


FIGURE 3. Key NOE data supporting the structure of **58**.

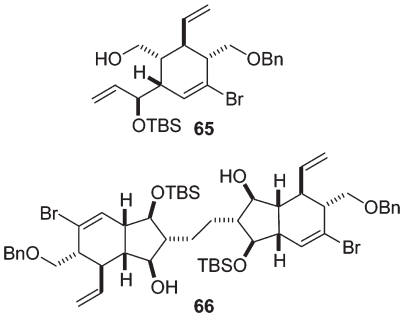


FIGURE 4. Alternative products of reductive cyclization.

when 2 equiv of the radical anion react together to form a new carbon−carbon bond. Formation of dimers in SmI_2-promoted reactions is known[25] and is due to the relative concentrations of the radical anion and SmI_2. On this occasion, a solution of SmI_2 was added slowly to a solution of **57**, and the blue coloration of the organometallic reagent dissipated rapidly, suggesting the SmI_2 was being consumed instantly. The resulting radical anion could not react with a second equivalent of SmI_2 because its concentration was very low, and instead, the radical anions self-condensed to form a dimer **66**. Inverse addition suppressed the formation of the dimer, but it was always isolated in small quantities even when the addition of the aldehyde was gradual. Changing the proton source to H_2O also suppressed the formation of this undesired dimer **66** (15%) and delivered **58** in 46% yield.

In the *t*-BuOH-containing reductive cyclization of aldehyde **57**, the protonation is an ionic intermolecular event between the organosamarium and *t*-BuOH. As some alcohols and water are known to displace bulk solvent (THF) and ligate the samarium center in the absence of HMPA[27] (where *t*-BuOH is not), the use of water as proton donor introduces the possibility the water is activating the samarium so that after cyclization the resulting radical is reduced more rapidly to the anion. This anion can then be protonated in an

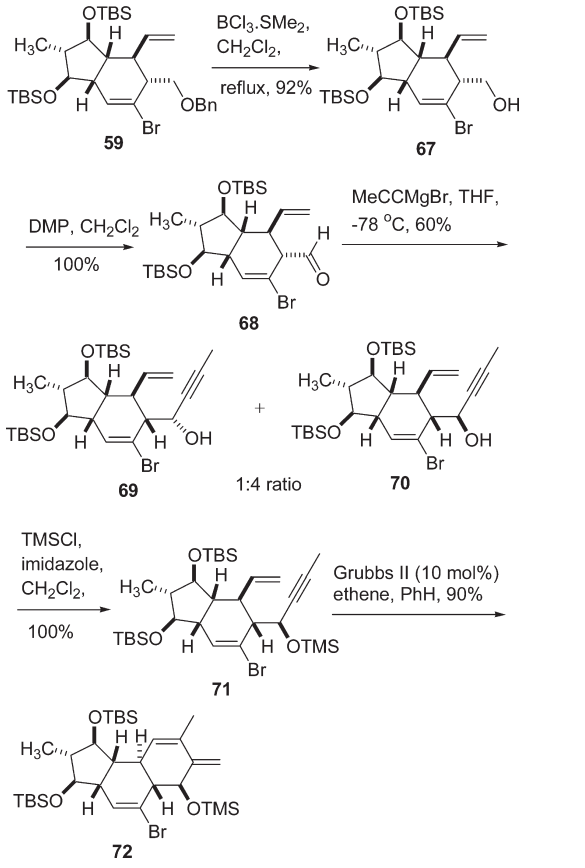
(23) Fetizon, M.; Jurion, M. *J. Chem. Soc., Chem. Commun.* **1972**, 382.
(24) Grové, J. J.; Holzapfel, C. W.; Williams, D. B. G. *Tetrahedron Lett.*, **1996**, *37*, 1305 and 5817.
(25) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132.
(26) Chopade, P. R.; Prasad, E.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2004**, *126*, 44.
(27) Hasegawa, E.; Curran, D. P. *J. Org. Chem.* **1993**, *58*, 5008.

intramolecular fashion by the water coordinated to the samarium.

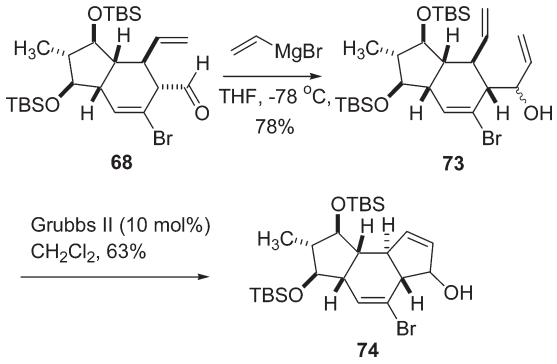
With it established that use of HMPA and H_2O led to improvements in the yield of **58**, the next set of conditions combined both of these additives and led to the formation of **58** in an improved 59% yield with only 6% of dimer **66** being formed. Despite this improvement in yield it was sought to increase the yield of **58** further and to this end the use of lithium halide additives as reported by Flowers were investigated.[28] Flowers had shown that premixing SmI_2 and LiBr produced $SmBr_2$ in situ, which was shown to be a more powerful reductant than SmI_2 alone and similar in strength to SmI_2−HMPA. It was hoped that good yields of **58** could achieved without the need for the carcinogenic additive HMPA. Preforming $SmBr_2$ followed by addition of this material to a solution of **57** and water led to the rapid consumption of starting material and the isolation of **58** in only 26% yield from a complex reaction mixture; however, as there was no trace of dimer formation with this additive system it was investigated further. Alternatively, if LiBr was used as an additive, i.e., a solution of **57**, H_2O, and LiBr was treated with a solution of SmI_2, the desired **58** was isolated as the major product in 64% yield with a trace of another diastereomer, which proved too unstable to characterize unambiguously. It had previously been postulated that water competed with HMPA to coordinate to the samarium center, which activated the samarium species and promoted reduction of the primary radical, which consequently suppressed dimer formation. When LiBr was the additive this effect was magnified as no dimer was formed. To coordinate to the metal center, water was competing with THF, iodide, and bromide ions, all of which have a much lower affinity for lanthanides than HMPA. Therefore, it is postulated water was able to coordinate more effectively with the samarium atom, thus promoting reduction of the radical to the anion, which subsequently suppressed dimer **66** formation completely. With the optimized formation of **58** complete the free hydroxyl group was silylated quantitatively with TBSOTf to give **59**, the structure of which was confirmed by single-crystal X-ray analysis (see Figure 2 in the Supporting Information).

The annulation of the C-ring onto the AB-ring system could now be attempted (Scheme 14). The benzyl group was removed with $BCl_3 \cdot SMe_2$ in 92% yield, and the resultant alcohol **67** was oxidized quantitatively with Dess−Martin periodinane to the aldehyde **68**. Aldehyde **68** proved to be relatively unstable so upon isolation it was reacted immediately with propynylmagnesium bromide to furnish a 4:1 mixture of diastereomeric alcohols **69** and **70**, which could be separated by flash column chromatography to give **69** in 6% yield and **70** in 54% yield. The major diastereomer was protected as the TMS ether and then subjected to enyne metathesis under our previous conditions. However, we were gravely disappointed to find that the product of enyne metathesis of **71** was **72** which contained the undesired 6-membered C-ring we had seen previously in the enyne metathesis of **32**. We had hoped that the presence of a silyl ether would promote formation of the desired 5-membered ring, as we had observed with enyne **30**. Sadly, this was not

SCHEME 14. Preparation of C-Ring Precursor Substrates



SCHEME 15. Synthesis of the ABC-Rings of Hexacyclinic Acid 1



the case, and we are currently unable to explain this change in reactivity, although we postulate that it may be due to differences in the conformations between **30** and **71**, or the possible co-ordinating effect of the lactone carbonyl in **30** directing the catalyst to the olefin first.[29]

With enyne metathesis failing to give the desired ring system it was decided to resort to a simple ring closing olefin metathesis which had been used in the model compound **27**. To this end **68** was treated with vinylmagnesium bromide to give **73** (Scheme 15) as a mixture of diastereomers, which were not separated, in 78% yield. The diastereomeric mixture **73** was subjected to Grubbs' II catalyst which generated

(28) Miller, R. S.; Sealy, J. M.; Shabangi, M.; Kulman, M. L.; Fuchs, J. R.; Flowers, R. A. II. *J. Am. Chem. Soc.* **2000**, *122*, 7718.

(29) Grubbs, R. H. Personal communication.

the desired ABC-ring system **74** of hexacyclinic acid in a respectrable 63% yield.

Conclusion

We have executed a synthesis of the ABC-rings of hexacylinic acid, with suitable functionality on the C-ring to enable the annelation of a DEF-ring precursor unit. En route to the ABC-rings we have uncovered some subtle effects governing the selectivities of both the SmI_2 mediated cyclization reactions we used to form the AB-ring and in the ring-closing enyne metathesis we used to close the C-ring. In the case of the SmI_2 cyclization, we believe that the change in selectivity is due to the co-ordination of the proton donor to the Sm metal center. In the case of the metathesis reaction it would seem that subtle conformational changes, or again co-ordination of the catalyst to nearby functionality, affects the course of the reaction. Annulation of this unit and studies aimed at completing the synthesis of hexacyclinic acid are underway and will be reported in due course.

Experimental Section

Ethyl (4a*S,5*R**,6*R**,8a*R**)-3-Benzyl-6-[(benzyloxy)methyl]-7-bromo-3,4,4a,5,6,8a-hexahydro-4-oxo-1*H*-benzo[1,2]oxazine-5-carboxylate (11) and Ethyl (4a*S**,5*R**,6*S**,8a*S**)-3-Benzyl-6-[(benzyloxy)methyl]-7-bromo-3,4,4a,5, 6,8a-hexahydro-4-oxo-1*H*-benzo[1,2]oxazine-5-carboxylate (12).** To a solution of hydroxamic acid **10** (238 mg, 0.956 mmol), bromodiene **8** (226 mg, 0.797 mmol), and PPh_3 (313 mg, 1.20 mmol) in dry THF (20 mL) at 0 °C under N_2 was added TBAD (367 mg, 1.59 mmol), and the resulting orange-brown solution was allowed to warm to rt over 1 h and then stirred at rt for 72 h. Concentration in vacuo left a viscous brown oil that was purified immediately. Flash chromatography (hexane−Et_2O, 1:1) gave a pale yellow oil **12** (173 mg, 42%) and a yellow oil **11** (153 mg, 37%). Data for **12**: ν_{max}/cm^{-1} (film) 3063, 3031, 2979, 2927, 2869, 1727, 1645, 1453, 1367, 1269, 1160, 1107; δ_H (400 MHz, $CDCl_3$) 7.37−7.27 (10H, m), 5.96 (1H, dd, J = 2.0, 1.0 Hz), 5.02 (1H, d, J = 15.0 Hz), 4.49 (1H, d, J = 12.0 Hz), 4.43 (1H, d, J = 15.0 Hz), 4.42 (1H, d, J = 12.0 Hz), 4.18 (1H, dq, J = 10.5, 7.0 Hz), 4.06 (1H, dq, J = 10.5, 7.0 Hz), 3.97 (1H, dd, J = 9.5, 9.5 Hz), 3.73 (1H, dd, J = 10.0, 6.0 Hz), 3.58 (1H, dd, J = 10.0, 2.0 Hz), 3.55 (1H, dd, J = 9.5, 9.5 Hz), 3.41 (1H, dd, J = 12.0, 12.0 Hz), 3.10 (1H, dd, J = 12.0, 6.0 Hz), 3.02 (1H, ddddd, J = 6.0, 6.0, 2.0, 2.0, 1.0 Hz), 2.54 (1H, ddddd, J = 12.0, 9.5, 9.5, 2.0, 2.0 Hz), 1.24 (3H, t, J = 7.0 Hz) ppm; δ_C (100 MHz, $CDCl_3$) 172.8, 171.7, 138.0, 136.1, 128.7, 128.4, 128.2, 128.2, 127.9, 127.5, 127.5, 123.1, 73.1, 72.6, 68.3, 60.8, 49.7, 45.9, 42.7, 40.3, 37.0, 14.0 ppm; m/z (CI) 485 and 483 (1:1, $M^+ - CH_2O$), 470 and 468 (1:1, $M^+ - OC_2H_5$), 434 (M^+ − Br), 424 and 422 (1:1, $M^+ - CH_2C_6H_5$), 394 and 392 (1:1, $M^+ - CH_2OCH_2C_6H_5$), 378 and 376 (1:1, $M^+ - CH_2O - OCH_2C_6H_5$); found 514.1228, M + H^+, $C_{26}H_{29}{}^{79}BrNO_5$ requires 514.1224. Data for **11**: ν_{max}/cm^{-1} 2982, 2924, 2870, 1724, 1643, 1454, 1368, 1305, 1105; δ_H (500 MHz, $CDCl_3$) 7.38−7.27 (10H, m), 6.01 (1H, dd, J = 4.0, 1.5 Hz), 4.91 (1H, d, J = 15.0 Hz), 4.47 (1H, d, J = 11.5 Hz), 4.47 (1H, d, J = 15.0 Hz), 4.42 (1H, d, J = 11.5 Hz), 4.16 (2H, q, J = 7.0 Hz), 4.05 (1H, dd, J = 11.5, 4.0 Hz), 3.92 (1H, dd, J = 3.5, 3.5 Hz), 3.91 (1H, dd, J = 11.5, 4.0 Hz), 3.68 (1H, dd, J = 9.5, 3.5 Hz), 3.34 (1H, dd, J = 8.0, 3.5 Hz), 3.33 (1H, dd, J = 9.5, 8.5 Hz), 3.22 (1H, ddddd, J = 8.5, 3.5, 3.5, 1.5, 1.5 Hz), 3.01 (1H, ddddd, J = 8.0, 4.0, 4.0, 4.0, 1.5 Hz), 1.25 (1H, t, J = 7.0 Hz) ppm; δ_C (100 MHz, $CDCl_3$) 173.1, 167.4, 138.1, 135.8, 129.5, 128.5, 128.3, 128.3, 127.8, 127.7, 127.5, 124.2, 73.0, 72.7, 69.9, 61.4, 50.6, 44.3, 42.6, 37.3, 36.2, 14.1 ppm; m/z (ES) 538 and 536 (1:1, M + Na^+), 516 and 514 (1:1, M + H^+), 408 and 406 (1:1, $M^+ - OCH_2C_6H_5$). Anal. Calcd for $C_{26}H_{28}BrNO_5$: C, 60.71; H, 5.49; N, 2.72. Found: C, 60.46; H, 5.50; N, 2.90.

(3a*R,5a*R**,8a*R**,8b*R**)-5-Bromo-6-[(triethylsilyl)oxy]-7-(prop-1′-en-2′-yl)-3,3a,5a,6-tetrahydro-8a*H*-indeno[4,5-*c*]furan-1(8b*H*)-one (31).** A solution of **30** (8.6 mg, 20.2 μmol) and Grubbs' II generation catalyst (5.1 mg, 6.0 μmol) in benzene (2 mL) was heated under reflux under an ethene atmosphere for 1 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and purified by flash column chromatography (6:1 pentate−Et_2O) to give a colorless oil (6.1 mg, 71%). Data reported for the major diastereoisomer: ν_{max}/cm^{-1} (film) 2956, 2912, 2876, 1784, 1640, 1376, 1265, 1239, 1170, 1143, 1016, 739; δ_H (500 MHz; $CDCl_3$) 5.99 (1H, s), 5.90 (1H, t, J = 2.5 Hz), 5.29 (1H, s), 5.12 (1H, ddd, J = 8.8, 2.2, 1.2 Hz), 5.06 (1H, s), 4.55 (1H, t, J = 9.1 Hz), 4.01 (1H, t, J = 9.1, Hz), 3.37 (1H, qt, J = 9.1, 2.5 Hz), 2.78 (1H, dd, J = 12.7, 9.1 Hz), 2.76 (1H, m), 2.58 (1H, dd, J = 12.7, 10.5 Hz), 1.89 (3H, s), 0.94 (9H, t, J = 7.9 Hz), 0.64 (6H, q, J = 7.9 Hz) ppm; δ_C (125 MHz; $CDCl_3$) 176.7, 149.8, 137.4, 126.2, 124.3, 124.3, 115.1, 79.3, 70.8, 57.4, 44.1, 42.8, 39.3, 21.1, 7.2, 6.4 ppm; m/z (ES+) 447, 449 (1:1, M + Na^+); found 447.0962, M + Na^+ $C_{20}H_{29}{}^{79}BrNaO_3Si$ requires 447.0967.

(1*R,2*R**,3*S**,3a*R**,4*R**,5*R**,7a*R**)-5-[(Benzyloxy)methyl]-6-bromo-1-[(*tert* butyldimethylsilyl)oxy]-2-methyl-4-vinyl-2,3,3a,4,5,7a-hexahydro-1*H*-indene-3-ol (58).** A mixture of samarium powder (225 mg, 1.50 mmol) and diiodoethane (283 mg, 1.00 mmol) was evacuated, purged with N_2 (×3), and then treated with dry degassed THF (1 mL). The mixture was stirred vigorously at rt (CARE: exotherm and gas evolution) until the solution turned dark blue. The solution was stirred for 30 min, and then dry degassed THF (9 mL) was added to form a 0.1 M solution of SmI_2. Nitrogen was bubbled through a solution of HMPA (555 μL, 3.19 mmol) and water (239 μL, 13.3 mmol) in THF (5 mL) for 1 h. Separately, N_2 was bubbled through a solution of aldehyde **57** in dry THF (15 mL) for 1 h. To the first solution was added the THF solution of SmI_2 via cannula, and the resulting purple solution was cooled to −78 °C under N_2. To this was added the second THF solution at a rate of 0.5 mL min^{-1}. The solution was stirred for 5 min then it was opened to the atmosphere and allowed to warm to rt over 30 min. The solution was diluted with Et_2O (50 mL), then washed with water (6 × 20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to leave a crude yellow oil (72.7 mg, overweight). Flash chromatography (gradient [20−50%] Et_2O in pentane) afforded a pale yellow oil **58** (39.5 mg, 59%) and a yellow oil **66a** and **66b** (4.1 mg, 6%). Data for **58**: ν_{max}/cm^{-1} (solution; $CHCl_3$) 3607, 3031, 2956, 2928, 2857, 1640, 1602, 1258, 1122, 1050, 1028, 835; δ_H (500 MHz, $CDCl_3$) 7.36−7.28 (5H, m), 6.28 (1H, dd, J = 5.0, 2.5 Hz), 5.58 (1H, ddd, J = 17.0, 9.5, 9.5 Hz), 5.15 (1H, dd, J = 9.5, 1.0 Hz), 5.09 (1H, dd, J = 17.0, 1.0 Hz), 4.55 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 3.84 (1H, dd, J = 9.5, 2.5 Hz), 3.60 (1H, dd, J = 9.5, 2.5 Hz), 3.41 (1H, dd, J = 9.0, 4.0 Hz), 3.35 (1H, dd, J = 9.0, 9.0 Hz), 2.57 (1H, dddd, J = 9.0, 9.0, 5.0, 2.5 Hz), 2.42 (1H, ddd, J = 10.5, 9.5, 9.5 Hz), 2.28 (1H, ddddd, J = 9.5, 2.5, 2.5, 2.5, 2.5 Hz), 1.85 (1H, ddd, J = 10.5, 9.0, 4.0 Hz), 1.75 (1H, ddq, J = 9.0, 9.0, 7.0 Hz), 1.07 (3H, d, J = 7.0 Hz), 0.91 (9H, s), 0.08 (3H, s), 0.04 (3H, s) ppm; δ_C (125 MHz, $CDCl_3$) 140.1, 138.6, 131.6, 128.2, 127.6, 127.5, 125.1, 117.7, 81.3, 80.6, 73.1, 69.1, 50.4, 47.5, 46.3, 46.0, 44.6, 25.8, 17.9, 15.6, −4.1, −4.2 ppm; m/z (CI) 524.2187 (M + NH_4^+, $C_{26}H_{43}{}^{79}BrNO_3Si$ requires 524.2190), 531 and 529 (1:1, M + Na^+), 491 and 489 (1:1, M^+ − OH), 387 and 385 (1:1, $M^+ - CH_2OCH_2C_6H_5$).

A mixture of dimer isomers **66** (9.1 mg, 9.0 μmol) was purified by preparative TLC (CH_2Cl_2−Et_2O, 9:1) to deliver a pale yellow oil **66a** (4.1 mg, 45%) and a pale yellow oil **66b** (2.3 mg, 25%). Data for **66a**: ν_{max}/cm^{-1} (film) 3394 br, 2953, 2928, 2856, 1641, 1458, 1255, 1121, 1029, 1003, 837; δ_H (500 MHz, $CDCl_3$) 7.33−7.27 (5H, m), 6.27 (1H, dd, J = 4.5, 2.0 Hz), 5.54 (1H,

ddd, J = 17.0, 10.0, 10.0 Hz), 5.14 (1H, d, J = 10.0 Hz), 5.04 (1H, d, J = 17.0 Hz), 4.53 (1H, d, J = 12.0 Hz), 4.46 (1H, d, J = 12.0 Hz), 3.84 (1H, dd, J = 9.5, 2.0 Hz), 3.60−3.56 (2H, m), 3.43 (1H, dd, J = 9.0, 9.0 Hz), 2.60 (1H, dddd, J = 9.0, 9.0, 4.5, 2.0 Hz), 2.39 (1H, ddd, J = 10.0, 9.0, 9.0 Hz), 2.25 (1H, ddddd, J = 9.0, 2.0, 2.0, 2.0, 2.0 Hz), 1.91−1.79 (2H, m), 1.71 (1H, br ddd, J = 7.0, 7.0, 7.0 Hz), 1.28 (1H, m), 0.89 (9H, s), 0.06 (3H, s), 0.01 (3H, s) ppm; δ_C (125 MHz, $CDCl_3$) 139.9, 138.6, 131.6, 128.2, 127.6, 127.4, 125.3, 118.0, 81.4, 79.2, 73.1, 68.9, 55.5, 47.2, 46.6, 46.6, 44.0, 30.2, 25.9, 17.9, −4.1, −4.1 ppm; m/z (ES) 1033 ($M + Na^+$), 1037, 1035, and 1033 (1:2:1, $M + Na^+$), 1032, 1030, and 1028 (1:2:1, $M + NH_4^+$), 1015, 1013, and 1011 (1:2:1, $M + H^+$); found 1033.3455, $M + Na^+$, $C_{52}H_{76}{}^{79}Br_2NaO_6Si_2$ requires 1033.3439. Data for **66b**: ν_{max}/cm^{-1} (film) 3369 br, 2953, 2928, 2857, 1640, 1456, 1255, 1119, 1028, 1003, 837; δ_H (500 MHz, $CDCl_3$) 7.34−7.25 (5H, m), 6.27 (1H, dd, J = 5.0, 2.5 Hz), 5.56 (1H, ddd, J = 17.0, 9.5, 9.5 Hz), 5.16 (1H, dd, J = 9.5, 1.0 Hz), 5.07 (1H, dd, J = 17.0, 1.0 Hz), 4.54 (1H, d, J = 12.0 Hz), 4.47 (1H, d, J = 12.0 Hz), 3.85 (1H, dd, J = 9.5, 2.5 Hz), 3.61−3.59 (2H, m), 3.43 (1H, dd, J = 9.0, 9.0 Hz), 2.59 (1H, dddd, J = 9.0, 9.0, 5.0, 2.0 Hz), 2.41 (1H, ddd, J = 11.0, 9.5, 9.5 Hz), 2.26 (1H, ddddd, J = 9.5, 2.5, 2.5, 2.5, 2.5 Hz), 1.83 (1H, ddd, J = 11.0, 9.0, 3.0 Hz), 1.78−1.72 (2H, m), 1.40 (1H, m), 0.89 (9H, s), 0.06 (3H, s), 0.00 (3H, s) ppm; δ_C (125 MHz, $CDCl_3$) 140.0, 138.7, 131.6, 128.2, 127.5, 127.4, 125.3, 118.0, 81.0, 78.7, 73.1, 69.0, 55.9, 47.2, 46.6, 46.6, 43.9, 29.3, 25.9, 17.9, −4.1, −4.1 ppm; m/z (ES) 1037, 1035, and 1033 (1:2:1, $M + Na^+$), 1032, 1030, and 1028 (1:2:1, $M + NH_4^+$), 1015, 1013, and 1011 (1:2:1, $M + H^+$); found 1033.3440, $M + Na^+$, $C_{52}H_{76}{}^{79}Br_2NaO_6Si_2$ requires 1033.3439.

(1*S,2*S**,3*R**,3a*R**,5a*R**,8a*R**,8b*R**)-5-Bromo-1,3, di(*tert*-butyldimethyl silyl)oxy-1,2,3,3a,5a,6,8a,8b-octahydro-2-methylasindacen-13-ol (74).** To a solution of aldehyde **68** (66 mg, 0.125 mmol) in dry THF was added a 1 M solution of vinylmagnesium bromide in THF (0.37 mL, 0.37 mmol) at −78 °C, and the mixture was stirred for 2 h. After this the reaction was quenched with saturated aqueous NH_4Cl solution (6 mL) and the reaction mixture was extracted with ethyl acetate (3 × 40 mL), combined organics were washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated in vacuo give a brown oil. Flash column chromatography (petroleum ether/ethyl acetate (9:1)) afforded a clear oil **73** (54.2 mg, 78%) as an inseparable mixture of diastereoisomers, which were used without further purification. Nitrogen gas was bubbled through a solution of precursor **73** (26.7 mg, 0.048 mmol) in dry CH_2Cl_2 (2.5 mL) for 1 h. After this time, Grubbs' II catalyst (4 mg, 0.0048 mmol) was added, and reaction was stirred for 2 h at room temperature. Once the reaction had gone to completion (TLC), the solution was filtered through a plug of silica eluted with diethyl ether and concentrated in vacuo to yield a dark brown oil. Flash column chromatography (pentane/diethyl ether 15:1) gave a product as a brown oil **74** (16.2 mg, 63%): ν_{max}/cm^{-1} (film) 2957, 2930, 3887, 2857, 1472, 1463, 1361, 1259, 1006; δ_H (500 MHz, $CDCl_3$) 6.04−6.03 (2H, m), 5.86 (1H, ddd, J = 4.5, 2.5, 1.5 Hz), 4.75 (1H, brd, J = 8.8 Hz), 3.51 (1H, dd, J = 8.0, 3.5 Hz), 3.32 (1H, dd, J = 9.5, 9.5 Hz), 2.70 (1H, dddd, J = 9.5, 9.5, 2.8, 2.8 Hz), 2.55 (1H, dddd, J = 8.8, 5.5, 2.8, 2.5 Hz), 2.29 (1H, m), 2.09 (1H, m), 1.82 (1H, ddq, J = 9.5, 8.0, 6.5 Hz), 1.26 (1H, s), 1.04 (3H, d, J = 6.5 Hz), 0.91 (9H, s), 0.88 (9H, s), 0.11(3H, s), 0.08 (6H, s), 0.03 (3H, s) ppm; δ_C (100 MHz, $CDCl_3$) 135.8, 131.9, 130.6, 120.2, 81.2, 81.0, 78.8, 59.4, 51.1, 50.4, 47.9, 25.9, 25.8, 18.0, 17.9, 15.8, −3.7, −3.8, −3.9, −4.1 ppm; m/z (ESI+) 531 and 529 (1:1, $M^+ + H$), 515 and 513 (1:1, $M^+ - OH$), 401 and 399 (1:1, $M^+ - OSi(CH_3)_2C(CH_3)_3$), found 529.2163, $C_{25}H_{46}{}^{79}BrO_3Si_2$ requires 529.2169.

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Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds not included in the Experimental Section; copies of ^1H and ^{13}C NMR for all new compounds; X-ray crystallographic CIF files for compounds **50** and **59**. This material is available free of charge via the Internet at http://pubs.acs.org.