JOC*Article*

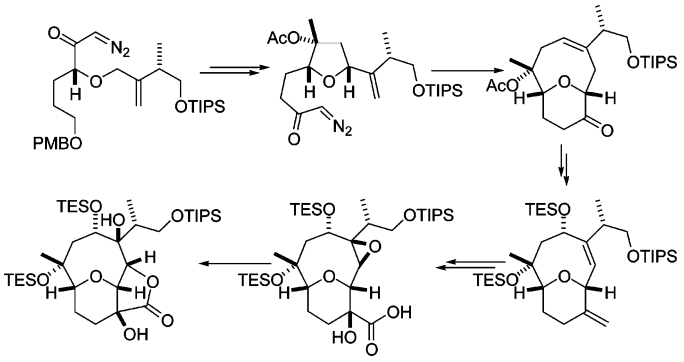
Stereoselective Construction of the Tricyclic Core of Neoliacinic Acid

J. Stephen Clark,*[,†] Carl A. Baxter,[‡] Alexander G. Dossetter,[‡] Stéphane Poigny,[‡] José L. Castro,[§,||] and William G. Whittingham[⊥]

WestCHEM, Department of Chemistry, Joseph Black Building, University of Glasgow, University Avenue, Glasgow, G12 8QQ, United Kingdom, School of Chemistry, University of Nottingham, University Park, Nottingham, NG7 2RD, United Kingdom, Merck Sharp and Dohme, Neuroscience Research Centre, Terlings Park, Harlow, Essex, CM20 2QR, United Kingdom, and Crop Protection Research Chemistry, Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire, RG42 6EY, United Kingdom

stephenc@chem.gla.ac.uk

Received October 8, 2007



The tricyclic core of the plant-derived sesquiterpene natural product neoliacinic acid was synthesized using a novel synthetic strategy. The pivotal synthetic transformations are construction of the key bicyclic ether-bridged intermediate by sequential deployment of metal carbenoid C−H insertion and ylide-forming reactions and installation of the lactone portion of neoliacinic acid by an acid-catalyzed intramolecular ring-opening reaction of an epoxide with a carboxylic acid.

Introduction

Neoliacinic acid (**1**) is a highly oxidized sesquiterpene natural product, first isolated by acetone extraction of fresh leaves of the plant *Neolitsea acciculata* Koidz by Takaoka and co-workers in 1987.[1] It is one of several structurally related ether-bridged sesquiterpene lactones that have been isolated from a variety of plant sources worldwide over the past 35 years. Other members of this family of natural products include the epoxide **2**, isolated from a sample of the plant *Milleria quinqueflora* that had been collected in Costa Rica,[2] and badgerin (**3**), isolated from the Montana sagebrush *Artemesia arbuscula*.[3] The lactone **4** and tanargyrolide (**5**), which were isolated from *Tanacetum argyrophyllum* and possess significant anti-bacterial activity, also belong to this family of sesquiterpene natural products.[4]

Although little is known about the bioactivity of neoliacinic acid (**1**), the workers who first isolated the compound suggested that it might possess anti-tumor activity because neoliacine, a very closely related sesquiterpene isolated from the same plant, displays moderate cytotoxicity.[5] However, there have been no further reports concerning the bioactivity of neoliacinic acid,

* Corresponding author. Fax: 44-141-330-4888.
† University of Glasgow.
‡ University of Nottingham.
§ Merck Sharp and Dohme.
|| Current address: GlaxoSmithKline, Neurology CEDD, New Frontiers Science Park, Third Avenue, Harlow, Essex CM19 5AW, UK.
⊥ Syngenta.

(1) Takaoka, D.; Nozaki, H.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1987**, 1861−1862.
(2) Jakupovic, J.; Castro, V.; Bohlmann, F. *Phytochemistry* **1987**, *26*, 2011−2017.
(3) Shafizadeh, F.; Bhadane, N. R. *J. Org. Chem.* **1972**, *37*, 274−277.
(4) Gören, N.; Jakupovic, J.; Topal, S. *Phytochemistry* **1990**, *29*, 1467−1469.
(5) Nozaki, H.; Hiroi, M.; Takaoka, D.; Nakayama, M. *J. Chem. Soc., Chem. Commun.* **1983**, 1107−1108.

10.1021/jo702111u CCC: $40.75
Published on Web 01/03/2008

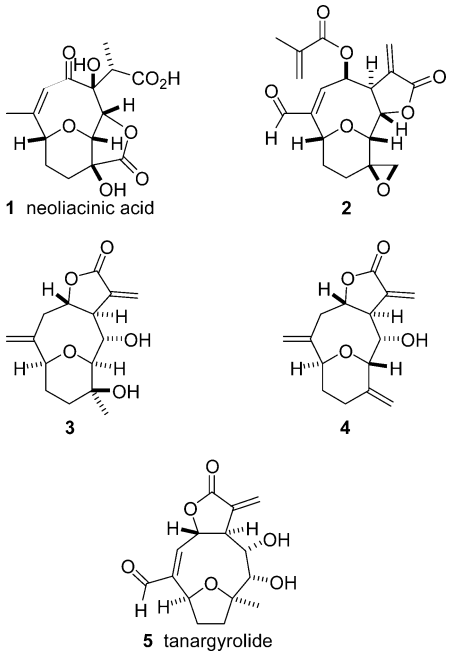


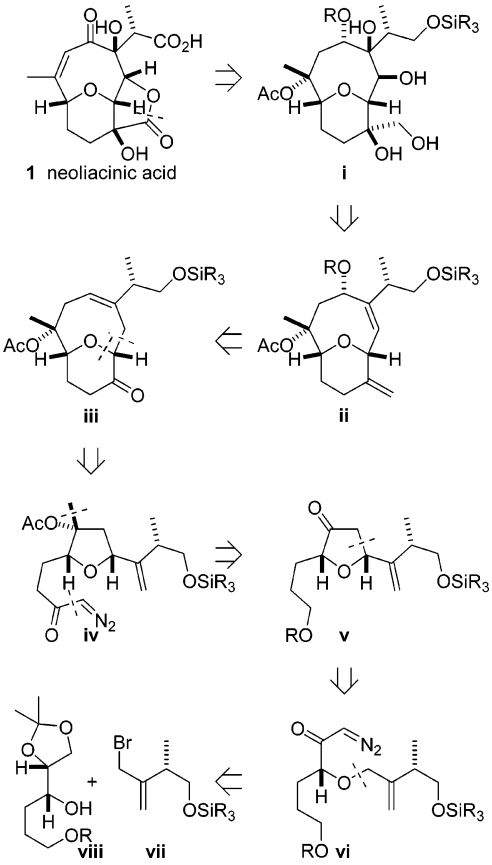
FIGURE 1. Various plant-derived sesquiterpene natural products possessing an ether bridged core.

and so at present, there is no evidence to suggest that the compound is a cytotoxic agent.

The complex ether-bridged tricyclic framework of neoliacinic acid (**1**) makes it a highly attractive but challenging synthetic target. The dense array of oxygen-containing functionalities at different oxidation levels coupled with the contiguous nature of the stereogenic centers that adorn the interlocking tricyclic core of the natural product presents a formidable challenge to current methods for ring construction and stereocontrol. In spite of the obvious attraction of neoliacinic acid as a target, there have been only two reports concerning synthetic endeavors toward this compound: our own preliminary synthetic work[6] and that of Paget and Paquette[7] concerning the construction of a functionalized 3-methylenetetrahydropyran as a potential building block for conversion into the natural product.

Over the past 15 years, we have explored the use of sequential one-pot catalytic carbenoid formation, intramolecular oxonium ylide generation, and ylide rearrangement to construct cyclic ethers in a diastereoselective manner.[8] We wished to employ this potentially powerful sequence as the key ring-forming reaction to construct the bridged bicyclic ether core of neoliacinic acid and so performed our retrosynthetic analysis to incorporate the corresponding disconnection. In studies performed since the publication of our preliminary work on neoliacinic acid,[6] we have used this key reaction sequence to construct the bridged ether cores of marine diterpene natural products of the cladiellin/eunicellin family; this work has

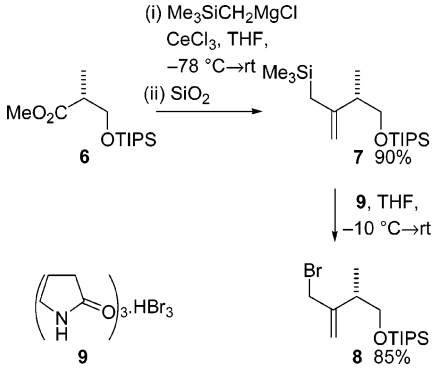
SCHEME 1. Retrosynthetic Analysis of Neoliacinic Acid



culminated in the total synthesis of (±)-vigulariol and the core ring system found in labiatin A.[9]

Retrosynthetic analysis of neoliacinic acid (**1**) incorporating the key ylide rearrangement strategy is shown in Scheme 1. It was anticipated that the natural product would be constructed from a late-stage intermediate corresponding to the polyhydroxylated ether-bridged bicyclic system **i** obtained by retrosynthetic opening of the lactone and various reductive functional group interconversions (FGIs) such as replacement of the enone with a 1,3-diol. The late-stage intermediate **i** possesses the six stereogenic centers found in neoliacinic acid (**1**) and all of the requisite oxygen functionality. This analysis requires introduc-

SCHEME 2. Synthesis of the Allylic Bromide 8



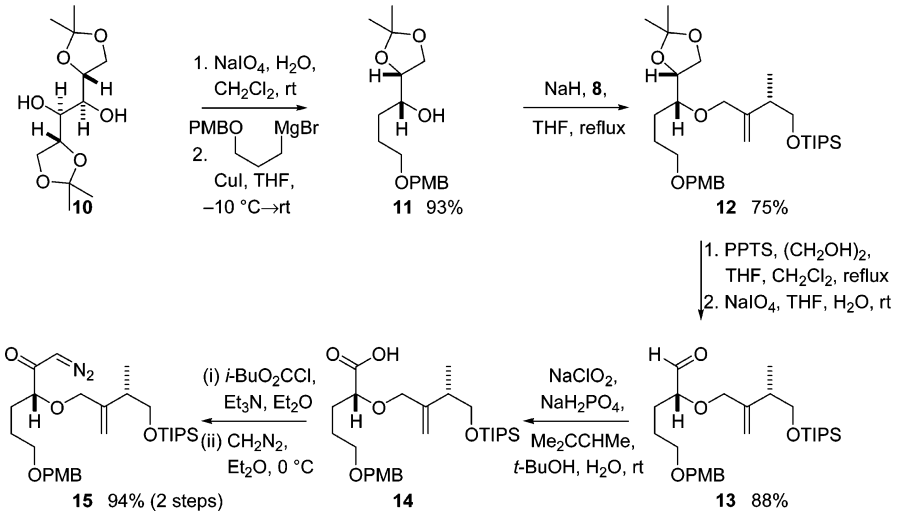
(6) (a) Clark, J. S.; Dossetter, A. G.; Blake, A. J.; Li, W. S.; Whittingham, W. G. *Chem. Commun*. **1999**, 749−750. (b) Clark, J. S.; Dossetter, A. G.; Whittingham, W. G. *Tetrahedron Lett.* **1996**, *37*, 5605−5608.

(7) Paget, S. G.; Paquette, L. A. *J. Indian Chem. Soc.* **1999**, *76*, 515−520.

(8) (a) Clark, J. S. *Tetrahedron Lett.* **1992**, *33*, 6193−6196. (b) Clark, J. S.; Krowiak, S. A.; Street, L. J. *Tetrahedron Lett.* **1993**, *34*, 4385−4388. (c) Clark, J. S.; Whitlock, G. A. *Tetrahedron Lett.* **1994**, *35*, 6381−6382. (d) Clark, J. S.; Whitlock, G.; Jiang, S.; Onyia, N. *Chem. Commun.* **2003**, 2578−2579. (e) Clark, J. S.; Fessard, T. C.; Wilson, C. *Org. Lett.* **2004**, *6*, 1773−1776.

(9) (a) Clark, J. S.; Hayes, S. T.; Wilson, C.; Gobbi, L. *Angew. Chem., Int. Ed.* **2007**, *46*, 437−440. (b) Clark, J. S.; Baxter, C. A.; Castro, J. L. *Synthesis* **2005**, 3398−3404.

SCHEME 3. Synthesis of the Diazo Ketone 15



tion of the enone and oxidation of the side chain late in the synthesis. The compound **i** possesses four free hydroxyl groups that correspond to two discrete 1,2-diol units. Recognition of this functionality suggests further disconnection by retrosynthetic double dihydroxylation, affording the diene **ii**. In a forward sense, it seemed likely that a double dihydroxylation reaction would lead to the required stereochemical outcome as a consequence of the conformational preference of the diene **ii**. Removal of the methylene group of the exocyclic alkene to reveal a ketone and conversion of the allylic alcohol into a transposed alkene then leads to the ketone **iii**, which would be the product arising from [2,3] rearrangement of the oxonium ylide generated by intramolecular trapping of a metal carbenoid derived from the diazo ketone **iv**. Further simplification produces the dihydro-3(2*H*)-furanone **v**, and a retrosynthetic carbenoid C−H insertion reaction then reveals the diazo ketone **vi**. The diazo ketone **vi** could be accessed from the relatively simple allylic bromide **vii** and alcohol **viii**, both of which should be readily available from simple chiral pool starting materials. Thus, two of the stereogenic centers would be obtained from the starting materials used to prepare intermediates **vii** and **viii**, and the other four stereogenic centers would be introduced using substrate control. In addition, the two key ring-forming reactions would be accomplished by exploiting two contrasting facets of metal carbenoid reactivity; two different catalysts would be used to control chemoselectivity.

Results and Discussion

The allylic bromide **8**, required for introduction of the side chain and corresponding to the fragment **vii** in the retrosynthetic analysis, was prepared first (Scheme 2). This bromide was synthesized in just two steps from a triisopropylsilyl-protected Roche ester (**6**). Treatment of the ester **6** with 3 equiv of the organocerium reagent generated by reaction of trimethylsilylmethylmagnesium chloride with anhydrous cerium(III) chloride[10] resulted in double Grignard addition.[11] Workup and exposure of the crude tertiary alcohol to silica gel facilitated Peterson elimination and delivered the allylic silane **7** in excellent yield.[11,12] Reaction of the allylic silane **7** with pyrrolidone hydrotribromide in THF, with careful control of temperature, then delivered the required allylic bromide **8**.[13]

The alcohol **11**, required for coupling to the allylic bromide **8**, was prepared from the commercially available D-mannitol-derived bis-acetonide **10** in high yield (Scheme 3). Periodate cleavage of the diol **10** afforded (*R*)-isopropylideneglyceraldehyde, which was then subjected to chelation-controlled addition of the organocopper reagent prepared from copper(I) iodide and 3-[(4-methoxybenzyl)oxy]propylmagnesium bromide.[14] The alcohol **11** was then coupled to the allylic bromide **8** using standard Williamson ether conditions to give the allylic ether **12**. Acid-catalyzed removal of the acetonide protecting group afforded the corresponding 1,2-diol, and treatment of this diol with sodium periodate resulted in oxidative cleavage and delivered the aldehyde **13** in excellent yield. A buffered chlorite oxidation reaction[15] then provided the carboxylic acid **14**, and conversion of this compound into the diazo ketone **15** was accomplished by treatment with isobutyl chloroformate and reaction of the resulting mixed anhydride with a large excess of ethereal diazomethane. The sequence of chlorite oxidation and diazo ketone formation was highly efficient (94% over two steps) and amenable to scale-up; multigram quantities of the diazo ketone **15** could be obtained using this route.

The first key ring-forming reaction in our synthetic route—intramolecular diastereoselective C−H insertion to produce the tetrahydrofuran—was now explored (Scheme 4).[16] The reaction is complicated by the fact that there is more than one potential site for C−H insertion of the intermediate carbenoid. In addition, competing cyclopropanation of the alkene and anomalous C−H

(10) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787−6790.

(11) (a) Narayanan, B. A.; Bunnelle, W. H. *Tetrahedron Lett.* **1987**, *28*, 6261−6264. (b) Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. T.-L. *Tetrahedron* **1989**, *45*, 5877−5886.

(12) Mickleson, T. J.; Koviach, J. L.; Forsyth, C. J. *J. Org. Chem.* **1996**, *61*, 9617−9620.

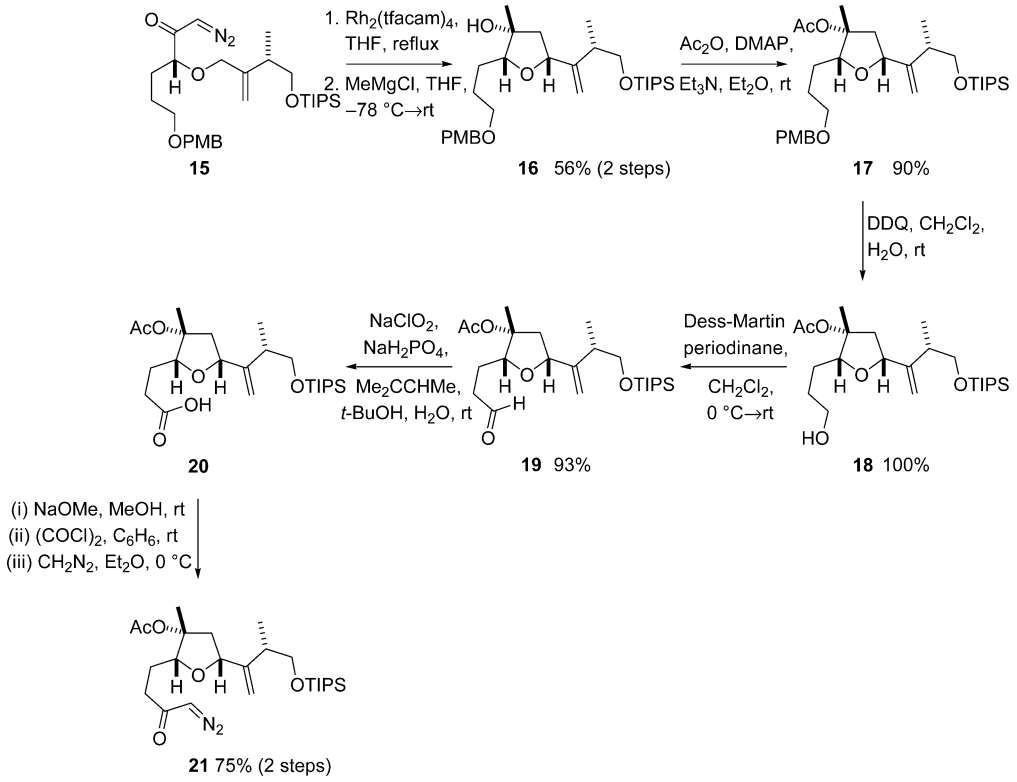
(13) (a) Grafstein, D. *J. Am. Chem. Soc.* **1955**, *77*, 6650−6651. (b) Awang, D. V. C.; Wolfe, S. *Can. J. Chem.* **1969**, *47*, 706−709.

(14) (a) Jackson, D. Y. *Synth. Commun.* **1988**, *18*, 337−341. (b) Sato, F.; Kobayashi, Y.; Takahashi, O.; Chiba, T.; Takeda, Y.; Kusakabe, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1636−1638.

(15) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(16) (a) Adams, J.; Frenette, R. *Tetrahedron Lett.* **1987**, *28*, 4773−4774. (b) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749−1752. (c) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753−1756. (d) Spero, D. M.; Adams, J. *Tetrahedron Lett.* **1992**, *33*, 1143−1146.

SCHEME 4. Synthesis of the Diazo Ketone 21



insertion of the carbenoid[17] are possible side reactions. The success of the reaction also requires stereoselective insertion of the carbenoid into one of the diastereotopic C−H bonds to deliver the required *cis* substituted cyclic ether. To circumvent these potential problems, we surveyed a wide range of rhodium(II) complexes. After extensive investigation of the reaction, we found that rhodium(II) trifluoroacetamide was the optimum complex for carbenoid generation;[17,18] the carbenoid generated from this complex in THF at reflux gave good levels of diastereocontrol while producing minimal amounts of other C−H insertion products and those arising from competing cyclopropanation.

The highest yields of the tertiary alcohol **16** were obtained when intramolecular C−H insertion and nucleophilic addition of the methyl fragment were performed without isolation of the intermediate ketone (cf. the ketone **v** in Scheme 1)—separation of the alcohol from minor byproducts arising during the C−H insertion reaction was more straightforward than at the ketone stage, and the alcohol **16** was more stable to purification. Originally, the methyl group was introduced by treatment of the intermediate ketone with trimethylaluminum,[19] but on scale-up, this procedure afforded only modest yields of the alcohol **16** (34% over two steps). Fortunately, when methylmagnesium chloride was used to install the methyl group, a substantially improved yield of the alcohol **16** (56% over two steps) was obtained on a >12 mmol scale. The Grignard addition reaction was highly diastereoselective, but it was difficult to gauge the exact level of diastereocontrol resulting from the addition of methylmagnesium chloride to the major C−H insertion product because several side products, including small amounts of those arising from the addition of methylmagnesium chloride to the minor *trans* disubstituted C−H insertion product, were obtained, and complete separation of the minor products was not possible.

Conversion of the alcohol **16** into the key cyclization precursor **21** was accomplished in five steps (Scheme 4). Acetylation of the tertiary alcohol **16** to give the acetate **17** followed by removal of the *p*-methoxybenzyl protecting group using 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) under aqueous conditions afforded the primary alcohol **18**. Oxidation of the primary hydroxyl group to give the aldehyde **19** was performed using the Dess−Martin periodinane,[20] and subsequent chlorite oxidation delivered the corresponding carboxylic acid **20**.[15] The diazo ketone **21** was then obtained by conversion of the sodium salt of carboxylic acid **20** into the corresponding acid chloride and subsequent treatment with an ethereal solution of diazomethane. The diazo ketone **21** required for the pivotal cyclization reaction could be prepared in >6 mmol scale using this protocol.

In the course of model studies[6b] and those involving related substrates,[8] we had established that copper(II) hexafluoroacetylacetonate was the catalyst of choice for the key oxonium ylide formation and rearrangement sequence. However, we needed to perform this reaction on a relatively large scale to obtain sufficient amounts of material to complete the latter stages of the synthesis. Using optimized reaction conditions (CH_2Cl_2 at reflux), the key cyclization reaction could be performed on a reasonable scale (6 mmol), giving gram quantities of the ether-

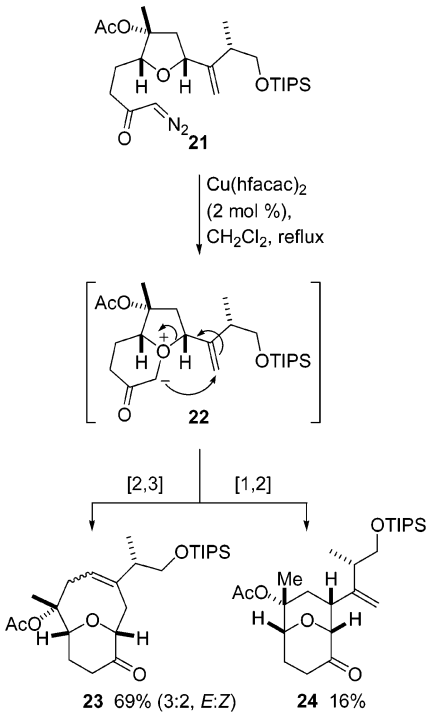
(17) (a) Clark, J. S.; Dossetter, A. G.; Wong, Y.-S.; Townsend, R. J.; Whittingham, W. G.; Russell, C. A. *J. Org. Chem.* **2004**, *69*, 3886−3898. (b) Clark, J. S.; Dossetter, A. G.; Russell, C. A.; Whittingham, W. G. *J. Org. Chem.* **1997**, *62*, 4910−4911.

(18) Dennis, A. M.; Korp, J. D.; Bernal, I.; Howard, R. A.; Bear, J. L. *Inorg. Chem.* **1983**, *22*, 1522−1529.

(19) (a) Ashby, E. C.; Laemmle, J. T. *Chem. Rev.* **1975**, *75*, 521−546. (b) Nicoloau, K. C.; Duggan, M. E.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 6666−6675.

(20) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.

SCHEME 5. Ylide Formation and Rearrangement to Give the Oxabicyclic Ketone 23

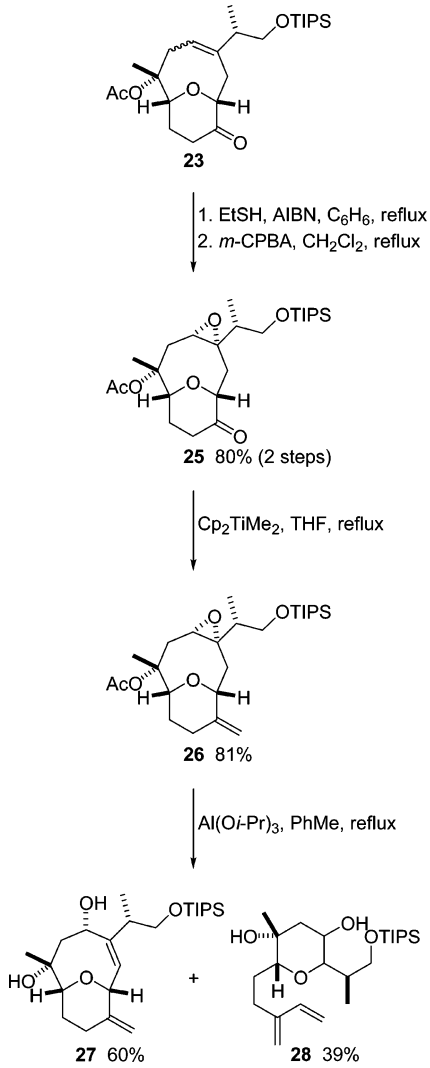


bridged compounds **23** and **24** in a combined yield of 85%, with the required [2,3] rearrangement product **23** (3:2, E/Z isomer mixture) predominating.

Successful construction of the oxabicyclo[5.3.1]undecane core of neoliacinic acid allowed introduction of the functionality required for construction of the third ring to be explored. The first issue to be addressed was isomerization of the mixture of alkenes **23** (Scheme 6). The thermodynamically favored *Z*-alkene was obtained in quantitative yield by exposure of the alkene mixture to ethanethiol and azobisisobutyronitrile (AIBN) in benzene at reflux.[21] Highly diastereoselective epoxidation of alkene ***Z*-23** was then accomplished using purified *m*-CPBA (to avoid competing Baeyer−Villiger oxidation), and the structure of the crystalline epoxide **25** was confirmed by X-ray crystallography.[6a]

The next objective was the regioselective ring opening of the epoxide to deliver an allylic alcohol corresponding to the intermediate **ii** in our retrosynthetic analysis (Scheme 1). In principle, the epoxide could be converted into an allylic alcohol either using a lithium amide base[22] or under Lewis acidic conditions.[23] Although methylenation of the ketone carbonyl group could be undertaken before or after conversion of the epoxide into an allylic alcohol, many of the reagents required to undertake the latter transformation are incompatible with the ketone carbonyl group, and so we opted to perform methylenation prior to introduction of the allylic alcohol. Methylenation of the ketone **25** to give the alkene **26** was accomplished in good yield using either dimethyltitanocene[24] or by employing the Nysted protocol.[25] However, the Petasis protocol proved to be the more reliable of the two methods, and so this method was employed routinely.[24]

SCHEME 6. Synthesis of the Allylic Alcohol 27

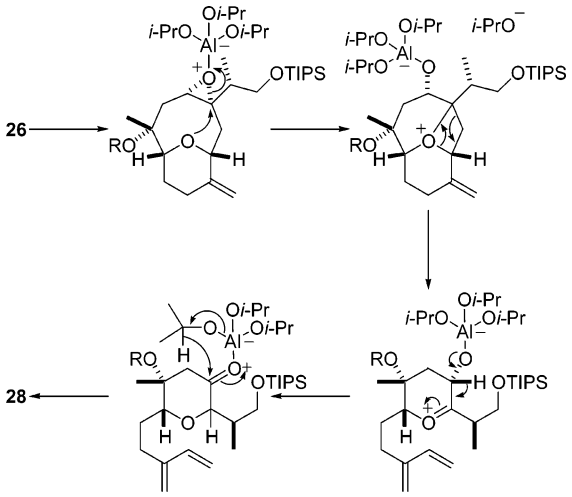


Conversion of the epoxide **26** into the required allylic alcohol was attempted using a wide range of Lewis acids and amide bases, but only one set of conditions delivered viable yields of the requisite allylic alcohol: treatment of the epoxide **26** with aluminum triisopropoxide in toluene at reflux afforded the allylic alcohol **27** (60% yield) with concomitant loss of the acetate group.[26] The unexpected tetrahydropyran diol **28** was also formed (5.5:1 mixture of two diastereomers) under the reaction conditions; this compound probably arises by Lewis acid complexation of the epoxide and nucleophilic attack by the bridging ether to give an oxonium ion, followed by sequential ring scission, hydride migration, and in situ Meerwein−Ponndorf−Verley reduction of the resulting complexed ketone (Scheme 7).[27]

The stage was now set for rapid introduction of much of the oxygen functionality that adorns the core of the natural product. The secondary and tertiary hydroxyl groups of the diol **27** were first protected as triethylsilyl ethers to afford the diene **29**

(21) Annunziata, R.; Cinquini, M.; Cozzi, F.; Gennari, C.; Raimondi, L. *J. Org. Chem.* **1987**, *52*, 4674−4681.
(22) Crandall, J. K.; Apparu, M. *Org. React.* **1983**, *29*, 345−443.
(23) Yasuda, A.; Tanaka, S.; Oshima, K.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1974**, *96*, 6513−6514.
(24) Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392−6394.
(25) Matsubara, S.; Sugihara, M.; Utimoto, K. *Synlett* **1998**, 313−315.
(26) Matsui, J.; Yokota, T.; Bando, M.; Takeuchi, Y.; Mori, K. *Eur. J. Org. Chem.* **1999**, 2201−2210.
(27) Hach, V. *J. Org. Chem.* **1973**, *38*, 293−299.

SCHEME 7. Proposed Reaction Mechanism for Formation of the Diene 28



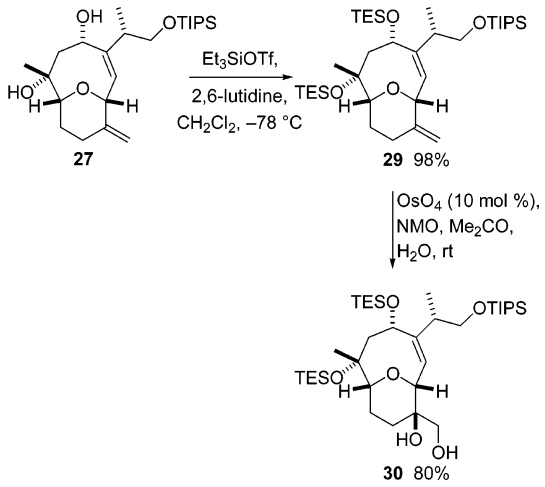
(Scheme 8). Initially, we had expected to perform simultaneous dihydroxylation of both alkenes in the diene **29** using osmium tetroxide. However, under standard conditions for catalytic dihydroxylation, in which a sub-stoichiometric amount of osmium tetroxide is used and *N*-methylmorpholine *N*-oxide is employed as the stoichiometric reoxidant,[28] the endocyclic trisubstituted alkene proved to be remarkably resistant to oxidation, and a clean and highly diastereoselective reaction of the exocyclic alkene was accomplished, delivering the diol **30** in good yield.

The unexpected formation of the diol **30** rather than the product arising from double dihydroxylation was a minor problem that necessitated reordering of some of the synthetic operations. We expected to be able to oxidize the primary hydroxyl group of the diol **30** to give the corresponding carboxylic acid and then perform dihydroxylation of the trisubstituted alkene followed by lactonization with inversion of configuration at the stereogenic center bearing the secondary hydroxyl group of the 1,2-diol.

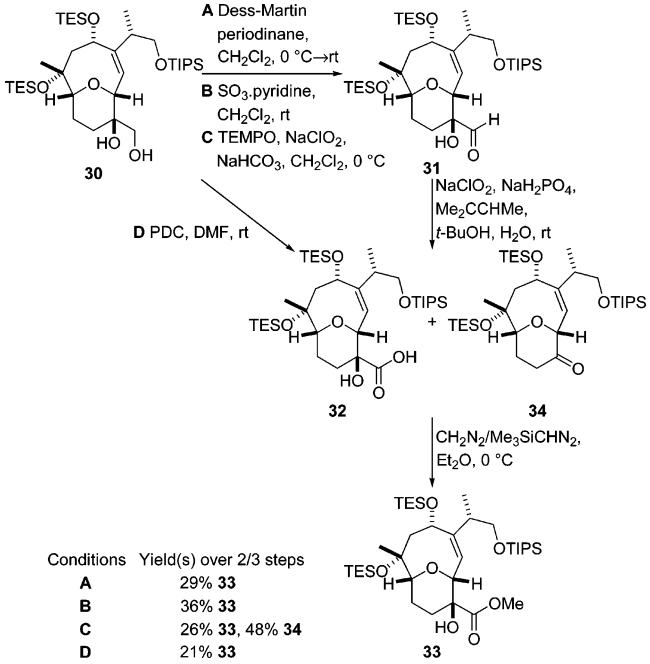
Various single (conditions D) and two-step oxidation procedures (conditions A−C) were investigated to oxidize the diol **30** and thus generate the carboxylic acid **32** (Scheme 9). However, this transformation proved to be extremely difficult to effect in high yield, and substantial decomposition was observed during isolation and storage of the carboxylic acid **32** or the intermediate aldehyde **31** (Scheme 9).[29] To circumvent this problem, it was necessary to convert the carboxylic acid **32** into the corresponding methyl ester **33** by immediate treatment with either diazomethane or trimethylsilyl diazomethane. The most consistent yields of the methyl ester **33** were obtained when diol **30** was oxidized sequentially using the Parikh−Doering procedure (conditions B),[30] followed by chlorite oxidation,[15] and the resulting carboxylic acid was immediately esterified using trimethylsilyl diazomethane.

The finding that modest yields are obtained when the diol **30** is oxidized to give the carboxylic acid **32** is consistent with reports of fragmentation during oxidation reactions of related

SCHEME 8. Synthesis of the Diol 30



SCHEME 9. Synthesis of the Hydroxy Ester 33



Conditions	Yield(s) over 2/3 steps
A	29% **33**
B	36% **33**
C	26% **33**, 48% **34**
D	21% **33**

vicinal diols.[29] The fact that a substantial amount of the ketone **34** was obtained from the sequence in which a TEMPO-mediated oxidation reaction (conditions C) was used to convert the diol **30** into the aldehyde **31**suggests that diol **30** undergoes cleavage during oxidation or that the intermediate aldehyde **31** is unstable.

The synthesis of the methyl ester **33**, albeit in modest yield, meant that the second dihydroxylation reaction could be performed (Scheme 10). In this case, stoichiometric quantities of osmium tetroxide and a large excess of pyridine were required to accomplish complete dihydroxylation of the sterically hindered and unreactive trisubstituted alkene.[28,31] The triol **35** was obtained as a single diastereoisomer in good yield from the dihydroxylation reaction—the ^{1}H NMR spectrum of this compound is diagnostic, showing an upfield shift for the methyl group of the ester from δ 3.80 to δ 3.35 ppm, possibly as a result of hydrogen bonding between the secondary hydroxyl group and the ester carbonyl group. In addition, one of the

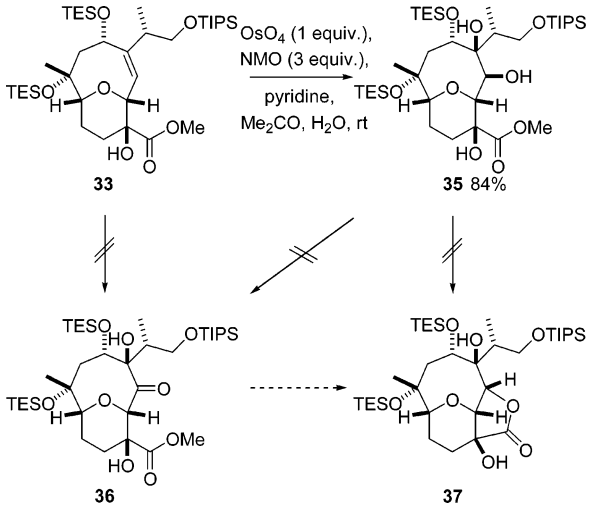
(28) For a review of alkene dihydroxylation using osmium tetroxide, see: Schröder, M. *Chem. Rev.* **1980**, *80*, 187−213.

(29) Aladro, F. J.; Guerra, F. M.; Moreno-Dorado, F. J.; Bustamante, J. M.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron Lett.* **2000**, *41*, 3209−3213.

(30) Parikh, J. R.; Doering W. v. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.

(31) Creigee, R. *Justus Liebigs Ann. Chem.* **1936**, *522*, 75−96.

SCHEME 10. Attempted Closure of the Lactone with Inversion of Configuration



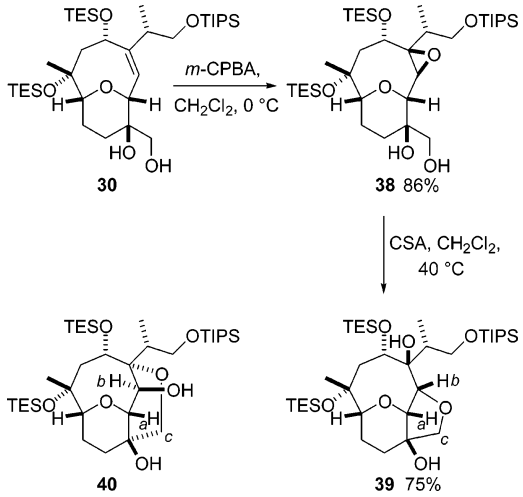
triethylsilyl groups displays restricted rotation, possibly indicating that the system is rigidified by hydrogen bonding.

To construct the lactone **37** possessing the stereochemistry found in neoliacinic acid (**1**), it was necessary to invert the configuration at the stereogenic center bearing the secondary hydroxyl group of the triol **35** (Scheme 10). Two approaches were conceivable: inversion of configuration prior to lactonization, or inversion during the lactonization reaction itself. Initially, inversion of configuration was attempted using an oxidation−reduction sequence, but the diol **35** was resistant to oxidation, and even direct formation of α-hydroxy ketone **36** from the alkene **33** was not successful.[32] Attempted activation of the secondary hydroxyl group using Mitsunobu conditions[33] or by formation of the cyclic sulfate of the 1,2-diol,[34] followed by S_N2 displacement with a variety of external oxygen nucleophiles or intramolecularly with the free carboxylic acid, also failed to deliver the lactone **37**.

From the previous results, it was clear that the secondary hydroxyl group of the triol **35** was extremely hindered and that it would not be possible to invert the configuration of the hydroxyl-bearing stereogenic center. This conclusion necessitated substantial revision of our synthetic plan to avoid the reaction sequence shown in Scheme 10. Reanalysis of the latter part of our synthetic strategy led us to investigate formation of the third ring by intramolecular nucleophilic opening of an epoxide rather than esterification or displacement of an activated alcohol.

The epoxide required for further studies was prepared by epoxidation of the alkene **30** (Scheme 11). Careful treatment of this alkene with *m*-CPBA resulted in highly diastereoselective epoxidation to give the epoxide **38** in 86% yield as a single diastereomer. The next step was intramolecular opening of the epoxide with the primary hydroxyl group, a reaction for which there are abundant literature precedents.[35] In the case of the

SCHEME 11. Closure of the Third Ring



epoxide **38**, the two possible modes of cyclization—5-exo-tet and 6-endo-tet—lead to two different products (**39** and **40**), and the conditions under which the reaction is performed are likely to have a considerable bearing on the outcome of the reaction. Initially, base-mediated cyclization to give the cyclic ether via a 5-exo-tet process was explored. However, treatment of the epoxy diol **38** with anionic bases, such as potassium *t*-butoxide and sodium hydride, or with the phosphazene bases developed by Schwesinger et al.,[36] failed to induce cyclization, and substantial quantities of starting material were recovered from these reactions.

Attention then turned to acid-mediated epoxide opening reactions, in spite of obvious concerns that the epoxide **38** might undergo competing 6-endo-tet cyclization at the more substituted position instead of the required 5-exo-tet reaction. Treatment of epoxide **38** with camphor sulfonic acid at 40 °C gave a single compound in 75% yield (Scheme 11).[35,37] Extensive NMR analysis (^{1}H, ^{13}C, DEPT, COSY, HMQC, and NOESY) of the product failed to establish which of the two possible products (**39** and **40**) had been produced. However, in an HMBC experiment, a three-bond coupling was observed between the carbon *c* and the protons *a* and *b*. This provides good evidence for the formation of the required tricyclic compound **39** rather than the 6-endo-tet product **40** because three-bond coupling between carbon *c* and proton *b* is not possible in the latter compound. The ^{1}H NMR spectrum of **39** has some other features that are worthy of note. First, the protons *a* and *b* are coupled with a *J* value of 4.7 Hz, whereas in the neoliacinic acid methyl ester, the corresponding protons couple with a *J* value of 4.0 Hz. The signals corresponding to protons at carbon *c* have also moved significantly in the ^{1}H NMR spectrum when compared to those in the starting epoxide **38** and now appear as two separate doublets at δ 3.96 and 3.36 ppm with a geminal *J* value

(32) (a) Lablanc, Y.; Black, W. C.; Chan, C. C.; Charleson, S.; Delorme, D.; Denis, D.; Gauthier, J. Y.; Grimm, E. L.; Gordon, R.; Guay, D.; Hamel, P.; Kargman, S.; Lau, C. K.; Mancini, J.; Ouellet, M.; Percival, D.; Roy, P.; Skorey, K.; Tagari, P.; Vickers, P.; Wong, E.; Xu, L.; Prasit, P. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 731−736. (b) David, K.; Greiner, A.; Goré, J.; Gazes, B. *Tetrahedron Lett.* **1996**, *37*, 3333−3334.

(33) Mitsunobu, O. *Synthesis* **1981**, 1−28.

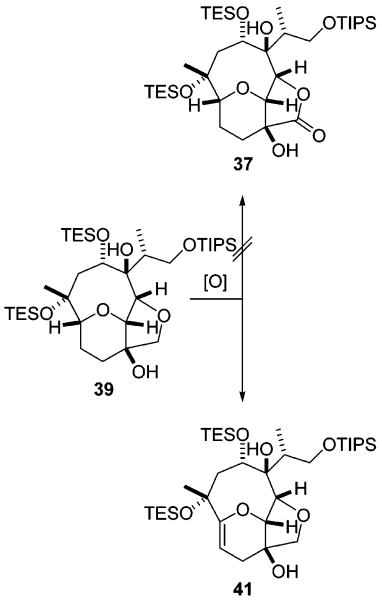
(34) Byun, H.-S.; He, L.; Bittman, R. *Tetrahedron* **2000**, *56*, 7051−7091.

(35) (a) Matsukura, H.; Morimoto, M.; Koshino, H.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 5545−5548. (b) Fujiwara, K.; Tokiwano, T.; Murai, A. *Tetrahedron Lett.* **1995**, *36*, 8063−8066. (c) González, I. C.; Forsyth, C. J. *Tetrahedron Lett.* **2000**, *41*, 3805−3807.

(36) (a) Schwesinger, R.; Schlemper, H. *Angew. Chem., Int. Ed.* **1987**, *26*, 1167−1169. (b) Schwesinger, R.; Hasenfratz, C.; Schlemper, H.; Walz, L.; Peters, E.-M.; Peters, K.; von Schnering, H. G. *Angew. Chem., Int. Ed.* **1993**, *32*, 1361−1363.

(37) Lanthanide triflates were also investigated as catalysts, but only trace amounts of the required cyclic ether **39** were obtained using $LaOTf_3$ or $ScOTf_3$. A 32% yield of **39** was obtained when the reaction was performed using $Cu(BF_4)_2$ in CH_2Cl_2 at room temperature.

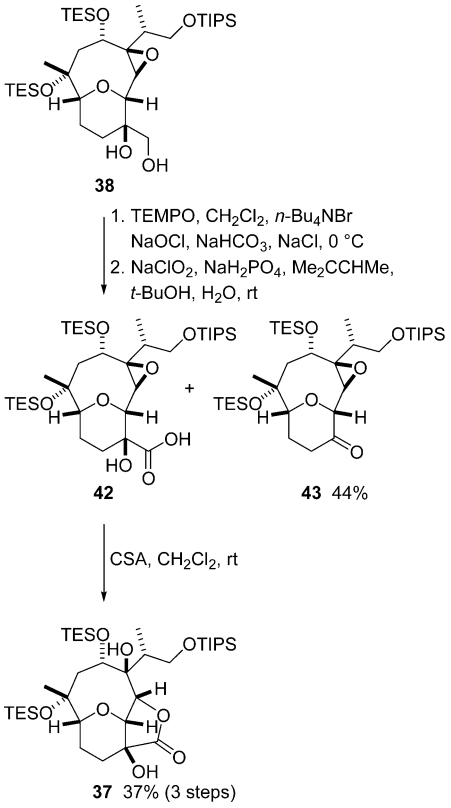
SCHEME 12. Attempted Oxidation of the Tricyclic Diol 39 to Form the Lactone 37



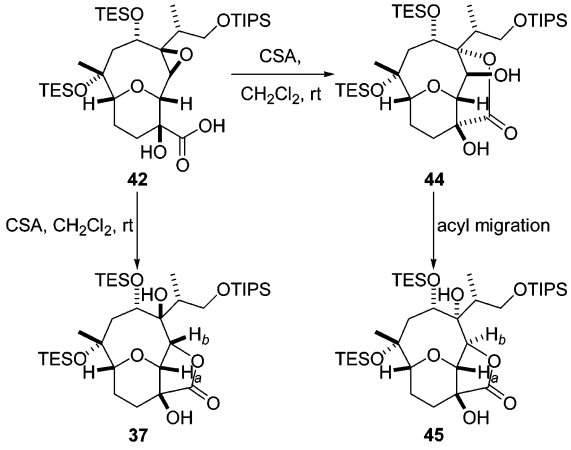
of 9.4 Hz, rather than as a single peak at 3.65 ppm. Only one of the hydroxyl group protons (that next to the side chain) can be detected in the ^{1}H NMR spectrum when it is obtained in either $CDCl_3$ (singlet δ 4.70 ppm) or C_6D_6, and the signal disappears when D_2O is added to the NMR sample.

The successful outcome of the cyclization reaction was significant because for the first time, we had constructed the complete tricyclic ring system of neoliacinic acid with all six of the stereogenic centers in place and with a high degree of stereocontrol. The next objective was the introduction of the lactone carbonyl group by oxidation of the methylene group present in the tetrahydrofuran portion of the tricyclic compound **39**. One particularly attractive method for performing this oxidation reaction involves the use of ruthenium tetroxide.[38] Paquette and co-workers successfully exploited this reaction to oxidize a structurally complex polycyclic substrate that was similar to our own, as the final step in their total synthesis of (+)-asteriscanolide,[39] and so we were reasonably confident that we could perform the same transformation on our compound. Various oxidative conditions to effect this transformation were investigated (Scheme 12). However, the lactone **37** was not obtained from any of these oxidation reactions, and instead, oxidation and subsequent elimination occurred at one of the bridgehead methine positions. Ruthenium tetroxide, prepared in situ from ruthenium(III) chloride and sodium periodate,[40] afforded the unexpected alkene **41** in 75% yield (based on recovered starting material). More esoteric reagents such as dimanganese heptoxide[41] delivered the same product (**41**), but in lower yield, whereas treatment of **39** with PCC[42] resulted in no reaction.

SCHEME 13. Closure of the Lactone 37



SCHEME 14. Possible Acid-Catalyzed 6-endo-tet Cyclization with Acyl Group Migration



These results were disappointing, but most literature examples of the direct oxidation of cyclic ethers to give lactones involve simple substrates, and few methods are available for the efficient oxidation of more complex furan-containing systems.[38]

It was not possible to oxidize a cyclic ether intermediate to produce the required lactone, and so clearly it was necessary to undertake the cyclization reaction using a substrate in which the correct oxidation level had already been achieved. In practice, this would mean effecting ring closure by opening the epoxide with a carboxylic acid or ester under acidic conditions (Scheme 13).[43] On the basis of the protocol employed to prepare

(38) Smith, A. B., III; Scarborough, R. M., Jr. *Synth. Commun.* **1980**, *10*, 205−211.

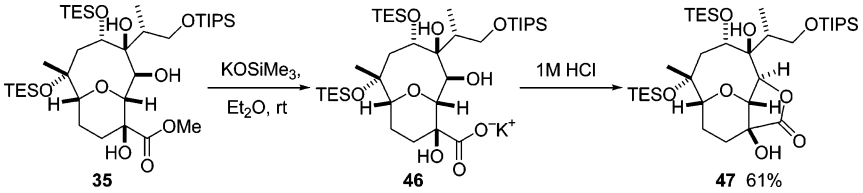
(39) Paquette, L. A.; Tae, J.; Arrington, M. P.; Sadoun, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 2742−2748.

(40) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936−3938.

(41) (a) Ito, K.; Fukuda, T.; Katsuki, T. *Heterocycles* **1997**, *46*, 401−411. (b) Trömel, M.; Russ, M. *Angew. Chem., Int. Ed.* **1987**, *26*, 1007−1009.

(42) (a) Bonini, C.; Iavarone, C.; Trogolo, C.; Di Fabio, R. *J. Org. Chem.* **1985**, *50*, 958−961. (b) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *31*, 2647−2650.

SCHEME 15. Formation of the Lactone 47 with Retention of Configuration



the methyl ester **33** (Scheme 9), a two-step TEMPO and chlorite oxidation sequence was used to give the acid **42**. Concerns regarding the instability of the intermediate carboxylic acid proved to be well-founded and prompted us to treat the crude product immediately with camphor sulfonic acid to give two products that were tentatively assigned as the lactone **37** and the bicyclic ketone **43**. The lactone **37** was formed in a 38% yield over three steps, with the fragmentation product **43** making up a significant proportion of the mass balance (44% yield). Several other oxidation procedures were investigated, but there was no improvement in yield of lactone **37** and an increased amount of the fragmentation product **43** was obtained in some cases.

In principle, both the 5-*exo* and the 6-*endo* modes of cyclization were possible, and so proving that constructing the lactone **37** was more difficult than expected. A peak at 1777 cm^{-1} was observed in the IR spectrum of the cyclization product, which is indicative of a five-membered lactone, but it is conceivable that two different five-membered lactones could be isolated from the acid-mediated cyclization reaction (Scheme 14). The lactone **37** arises from direct 5-exo cyclization of the acid onto the epoxide, giving the stereochemistry corresponding to that found in the natural product. The lactone **45** would arise from a 6-endo-tet cyclization to give the intermediate lactone **44** followed by acyl group migration to the less hindered secondary hydroxyl group. Unfortunately, ^{1}H NMR NOE experiments did not provide firm evidence on which to make an unambiguous structural assignment. However, the NMR data strongly suggest that the lactone **37** was formed because the magnitude of the coupling constant between the bridgehead proton H_a and the lactone ring junction proton H_b is comparable to that in the target compound (vide infra).

To obtain further evidence confirming the synthesis of the lactone **37**, the methyl ester **35** was treated with an excess of potassium trimethylsilanolate to afford the potassium carboxylate salt **46** (Scheme 15).[44] Acidic workup then resulted in cyclization to give the lactone **47**. The successful preparation of this new lactone along with the availability of the two tricyclic systems synthesized previously allowed ^{1}H NMR data for this series of compounds to be compared with that of methyl ester of the natural product (Figure 2). This comparison is very informative and reveals that the protons H_a and H_b in the cyclic ether **39** and the lactone **37** have similar coupling constants and that these correlate well with the corresponding coupling constant in the ^{1}H NMR spectrum of neoliacinic acid methyl ester (**48**). The lactone **47** shows a considerably larger coupling constant between the protons H_a and H_b, as expected. On the basis of this analysis, the lactone generated in Scheme 13 can be assigned as compound **37**. We are now confident that we have successfully prepared an advanced intermediate for the synthesis of neoliacinic acid. This key intermediate contains the entire tricyclic core of neoliacinic acid and possesses all six stereogenic centers with the correct configuration.

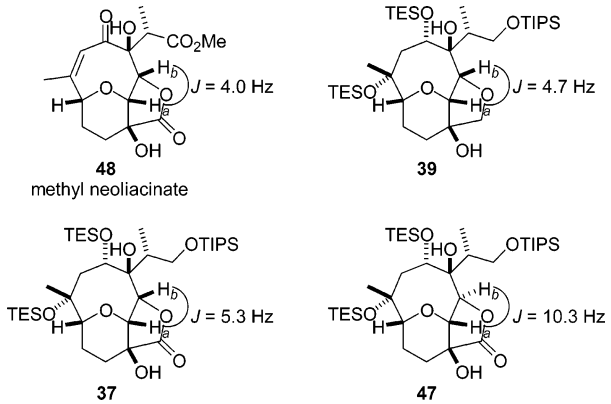


FIGURE 2. Comparison of key ring junction ^{1}H NMR coupling constants for the tricyclic compounds **37**, **39**, and **47** with that of methyl neoliacinate (**48**).

Conclusion

The fully functionalized tricyclic lactone core of the sesquiterpene natural product neoliacinic acid has been synthesized in a concise manner. Two metal carbenoid reactions—C−H insertion and oxonium ylide formation and rearrangement—were utilized to construct an oxabicyclic intermediate in an efficient manner. Formation of the lactone by ring closure onto the secondary hydroxyl of a 1,2-diol with inversion of configuration before or during cyclization was not possible. However, acid-catalyzed cyclization of a carboxylic acid onto an epoxide did deliver the required lactone along with a significant amount of the product resulting from cleavage of the sensitive α-hydroxy aldehyde/carboxylic acid unit. The lactone diol **37** was constructed in a total of 24 steps from (*R*)-(+)-2,3-isopropylidene glyceraldehyde and is the most advanced precursor to neoliacinic acid yet prepared, possessing all three rings and all six of the stereogenic centers present in the natural product.

Experimental Section

Methyl (*R*)-3-[(Triisopropysilyl)oxy]-2-methylpropionate (6). Triisopropylsilylchloride (36.5 mL, 171 mmol) was added over 10 min to a solution of methyl-(*R*)-(−)-3-hydroxy-2-methylpropionate (20.17 g, 170.7 mmol) and imidazole (23.25 g, 341.5 mmol) in dry DMF (60 mL) at room temperature under Ar. The mixture was stirred at room temperature for 5 days and then poured into a two phase mixture of water (70 mL) and ether (200 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 200 mL). The ether extracts were combined and washed with water (150 mL) and brine (100 mL), then dried ($MgSO_4$), and concentrated in vacuo to yield a clear oil. Vacuum distillation (86 °C at 0.5 mmHg) gave the silyl ether **6** (45.84 g, 98%) as a clear oil: $R_f = 0.56$ (petroleum ether-ethyl acetate, 19:1): $[\alpha]_D^{24}$

(43) For related examples of lactone formation by epoxide opening, see: (a) Paquette, L. A.; Sturino, C. F.; Wang, X.; Prodger, J. C.; Koh, D. *J. Am. Chem. Soc.* **1996**, *118*, 5620−5633. (b) Paquette, L. A.; Koh, D.; Wang, X.; Prodger, J. C. *Tetrahedron Lett.* **1995**, *36*, 673−676.

(44) Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831−5834.

−19.7 (c = 1.17, $CHCl_3$); ν_{max} ($CHCl_3$) 2944, 2891, 2866, 1732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.86 (1H, dd, J = 9.5, 6.7 Hz), 3.76 (1H, dd, J = 9.5, 6.0 Hz), 3.67 (3H, s), 2.66 (1H, qdd, J = 7.0, 6.7, 6.0 Hz), 1.15 (3H, d, J = 7.0 Hz), 1.10−0.98 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 65.8, 51.5, 42.8, 18.0, 13.5, 12.2; HRMS (CI, CH_4) m/z calcd for $C_{14}H_{31}O_3Si$ $[M + H]^+$ 275.2042, found 275.2045 (Δ 0.8 ppm). Anal. calcd for $C_{14}H_{30}O_3Si$: C, 61.26; H, 11.02. Found: C, 61.32; H, 10.82.

(*S*)-2-Methyl-1-[(triisopropylsilyl)oxy]-3-[(trimethylsilyl)methyl]but-3-ene (7). Cerium(III) chloride heptahydrate (61.46 g, 165.0 mmol) was added to a 1 L three-necked round-bottomed flask and dried under vacuum at 120 °C for 2 h and then at 160 °C for 2 h. The flask was allowed to cool and was purged with N_2 for 10 min, and dry THF (250 mL) was added. The mixture was stirred for 20 h at room temperature under N_2, and sonication (2 × 50 min) of the mixture then gave the cerium(III) chloride-THF complex as a white precipitate.

A solution of (chloromethyl)trimethylsilane (20.77 mL, 163.7 mmol) in dry THF (130 mL) was added dropwise to a stirred suspension of magnesium turnings (3.65 g, 150 mmol) and 1,2-dibromoethane (4 drops) in dry THF (30 mL) under N_2. Formation of the Grignard reagent was accomplished by heating the mixture to reflux, followed by slow addition of the halide to maintain reflux. The Grignard reagent was stirred at room temperature for 2 h and then added by cannula to the cerium(III) chloride-THF complex at −78 °C under N_2. The gray solution was stirred for 30 min, and then the ester **6** (13.72 g, 49.99 mmol) in dry THF (30 mL) was added (cannula) at −78 °C. The reaction was stirred at −78 °C for 2 h, the flask was then removed from the cold bath, and the mixture was stirred at room temperature for 15 h. The reaction mixture was cooled to 0 °C, a saturated solution of ammonium chloride (150 mL) was added at 0 °C, and the mixture was stirred for 20 min. Water (500 mL) was added, and the mixture was extracted with ether (3 × 300 mL). The combined ether extracts were washed with water (200 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. The oil was loaded onto a silica column and left on the column for 1 h before elution (petroleum ether then petroluem ether-ethyl acetate, 9:1) to give the allylic silane **7** (14.8 g, 90%) as a clear oil: R_f = 0.67 (100% hexane). $[\alpha]_D^{25}$ −22 (c = 0.50, $CHCl_3$); ν_{max} ($CHCl_3$) 2944, 2892, 2866, 1630, 882 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.62 (1H, t, J = 0.8 Hz), 4.58 (1H, t, J = 0.8 Hz), 3.75 (1H, dd, J = 9.4, 4.9 Hz), 3.42 (1H, dd, J = 9.4, 8.1 Hz), 2.13 (1H, dqd, J = 8.1, 7.0, 4.9 Hz), 1.58 (1H, dd, J = 13.6, 0.8 Hz), 1.56 (1H, dd, J = 13.6, 0.8 Hz), 1.12−1.01 (24H, m), 0.03 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.0, 106.3, 68.2, 43.8, 27.2, 18.2, 16.8, 12.1, −1.2; HRMS (EI) m/z calcd for $C_{18}H_{40}OSi_2$ $[M]^+$: 328.2618, found 328.2613 (Δ 1.3 ppm). Anal. calcd for $C_{18}H_{40}OSi_2$: C, 65.78; H, 12.27. Found: C, 65.71; H, 12.11.

(*S*)-3-Bromomethyl-2-methyl-1-[(triisopropylsilyl)oxy]but-3-ene (8). Pyrrolidone hydrotribromide (8.57 g, 17.3 mmol) was added to a stirred solution of the allylic silane **7** (5.68 g, 17.3 mmol) and pyridine (9 mL) in dry THF (732 mL) at −10 °C under Ar. The mixture was stirred for 2 h and allowed to warm to room temperature during this period. A saturated solution of sodium thiosulfate (100 mL) was added, and the mixture reduced in volume (ca. 100 mL) in vacuo. The mixture was diluted with ether (200 mL), and the aqueous layer was removed and extracted with further ether (200 mL). The ether extracts were combined and washed with water (100 mL) and brine (75 mL), then dried ($MgSO_4$) and concentrated in vacuo to deliver a yellow oil. Purification by column chromatography on silica gel (petroleum ether) gave the bromide **8** (4.91 g, 85%) as a clear oil: R_f = 0.22 (hexane); $[\alpha]_D^{25}$ −31.5 (c = 2.67, $CHCl_3$); ν_{max} ($CHCl_3$) 2941, 2891, 2866, 2725, 1829, 1638, 911, 883, 642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.26 (1H, d, J = 0.7 Hz), 5.03 (1H, s), 4.10 (1H, dd, J = 10.0, 0.7 Hz), 4.04 (1H, d, J = 10.0, 0.5 Hz), 3.71 (1H, dd, J = 9.5, 6.1 Hz), 3.65 (1H, dd, J = 9.5, 6.5 Hz), 2.60 (1H, qdd, J = 7.0, 6.5, 6.1 Hz), 1.14 (3H, d, J = 7.0 Hz), 1.11−1.04 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 114.9, 68.4, 39.6, 37.5, 18.1, 16.8, 12.0. Anal. calcd for $C_{15}H_{31}OSiBr$: C, 53.72; H, 9.32. Found: C, 53.98; H, 9.08.

(2*R*,3*R*)-1,2-*O*-Isopropylidene-6-[(4-methoxybenzyl)oxy]hexane-1,2,3-triol (11). A solution of 4-methoxybenzyl-3-bromopropyl ether (53.76 g, 207.5 mmol) in dry THF (200 mL) was added dropwise to a suspension of magnesium turnings (6.05 g, 249 mmol) and 1,2-dibromoethane (4 drops) in dry THF (30 mL) under N_2. Formation of the Grignard reagent was accomplished by heating the mixture to reflux followed by slow addition of the halide to maintain the reflux. The solution of the Grignard reagent was stirred at room temperature for 2 h and then was added (cannula) to a solution of copper(I) iodide (43.37 g, 227.7 mmol), dry dimethylsulfide (130 mL), and dry THF (600 mL) at −78 °C under N_2. The solution changed from a clear yellow to bright orange upon addition of the Grignard reagent. The mixture was stirred at −78 °C for 15 min, and then a solution of (*R*)-2,3-isopropylidene glyceraldehyde (18.0 g, 138 mmol) in dry THF (50 mL) was added over 5 min at −78 °C under N_2.[45] The mixture was allowed to warm to room temperature and was stirred for 15 h. The reaction was quenched by the addition of ice (ca. 2 g) followed by a saturated solution of ammonium chloride (500 mL) and ether (300 mL). The organic layer was removed, and the aqueous layer was extracted with further ether (2 × 200 mL). The ether extracts were combined and washed with water (300 mL) and brine (300 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 4:1 to 1:1) gave the alcohol **11** (39.78 g, 93%) as a clear oil: R_f = 0.07 (hexane-ethyl acetate, 4:1); $[\alpha]_D^{24}$ +15 (c = 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3580, 2987, 2936, 2885, 1612, 861 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.7 Hz), 6.87 (2H, d, J = 8.7 Hz), 4.43 (2H, s), 4.01−3.96 (2H, m), 3.79 (3H, s), 3.74−3.69 (1H, m), 3.53−3.48 (1H, m), 3.50−3.46 (2H, m), 2.67 (1H, s), 1.85−1.66 (2H, m), 1.57−1.44 (2H, m) 1.42 (3H, s), 1.36 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 130.4, 129.3, 113.8, 109.4, 79.2, 72.6, 72.0, 69.8, 66.1, 55.3, 30.6, 26.7, 26.0, 25.4; HRMS (APCI) m/z calcd for $C_{17}H_{26}O_5Na$ $[M + Na]^+$: 333.1678, found: 333.1681 (Δ 0.9 ppm). Anal. calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.43; H, 8.42.

(2*R*,3*R*)-1,2-*O*-Isopropylidene-6-[(4-methoxybenzyl)oxy]-3-{(3*S*)-3-methyl-2-methylene-4-[(triisopropylsilyl)oxy]butoxy}-hexane-1,2-diol (12). A solution of the alcohol **11** (6.13 g, 19.7 mmol) in dry THF (32 mL) was added to a stirred suspension of NaH (569 mg, 23.7 mmol) in dry THF (208 mL) at room temperature under N_2. The mixture was heated at reflux for 1 h under N_2, and then the bromide **8** (8.62 g, 25.7 mmol) in dry THF (81 mL) was added (cannula) under N_2. The reaction was heated at reflux for 24 h and then cooled to room temperature. The reaction was quenched by the addition of a saturated solution of ammonium chloride (20 mL) and water (100 mL). The reaction mixture was extracted with ether (3 × 200 mL), and the ether extracts were combined and washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 5:1) gave the acetonide **12** (8.39 g, 75%) as a clear oil: R_f = 0.28 (hexane-ethyl acetate, 9:1); $[\alpha]_D^{25}$ +14 (c = 0.90, $CHCl_3$); ν_{max} ($CHCl_3$) 2942, 2866, 1612, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J = 8.7 Hz), 6.86 (2H, d, J = 8.7 Hz), 5.09 (1H, s), 4.90 (1H, s), 4.42 (2H, s), 4.19 (1H, d, J = 12.6 Hz), 4.16 (1H, app. q, J = 6.5 Hz), 4.03 (1H, d, J = 12.6 Hz), 3.96 (1H, dd, J = 8.2, 6.5 Hz), 3.79 (3H, s), 3.72−3.66 (2H, m), 3.54 (1H, dd, J = 9.4, 7.3 Hz), 3.47−3.42 (2H, m), 3.35 (1H, ddd, J = 8.4, 6.3, 3.8 Hz), 2.37 (1H, dqd, J = 7.3, 6.9, 5.4 Hz), 1.85−1.74 (1H, m), 1.72−1.60 (1H, m), 1.58−1.40 (2H, m), 1.41 (3H, s), 1.34 (3H, s), 1.10 (3H, d, J = 6.9 Hz), 1.07−1.03 (21H,

(45) (*R*)-(+)-2,3-Isopropylidene glyceraldehyde was prepared according to the procedure of Jackson (ref 14a): $[\alpha]_D^{20}$ +79 (c = 1.0, $CHCl_3$), lit. $[\alpha]_D$ +63.3 (c = 1.25, C_6H_6).

m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 149.2, 130.7, 129.3, 113.8, 110.8, 109.3, 79.8, 78.3, 73.6, 72.6, 70.0, 68.0, 66.0, 55.3, 39.5, 27.4, 26.6, 26.0, 25.5, 18.1, 16.5, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{32}H_{56}O_6Si$ $[M]^+$: 564.3846, found: 564.3888 (Δ 7.3 ppm). Anal. calcd for $C_{32}H_{56}O_6Si$: C, 68.04; H, 9.99. Found: C, 67.93; H,10.02.

(2*R*)-5-[(4-Methoxybenzyl)oxy]-2-{(3*S*)-3-methyl-2-methylene-4-[(triisopropylsilyl)oxy]butoxy}pentanal (13). PPTS (1.36 g, 5.39 mmol) was added to a solution of the acetonide **12** (15.2 g, 26.9 mmol) in ethylene glycol (375 mL), THF (180 mL), and CH_2Cl_2 (180 mL), and the mixture was heated to reflux for 20 h. The reaction was allowed to cool to room temperature and was neutralized with concd ammonia solution (ca. 8 mL). The mixture was diluted with water (200 mL) and extracted with CH_2Cl_2 (3 × 200 mL). The organic extracts were combined and washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. The crude diol was dissolved in THF (225 mL) and water (90 mL), and then $NaIO_4$ (23.08 g, 107.9 mmol) was added at room temperature over 10 min. The mixture was stirred for 90 min at room temperature, and then water (700 mL) was added. The reaction mixture was extracted with ether (3 × 200 mL), and the combined ether extracts were washed with water (200 mL) and brine (200 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1) gave the aldehyde **13** (11.62 g, 88%) as a clear oil: R_f = 0.32 (hexane-ethyl acetate, 9:1); $[\alpha]_D^{21}$ +23 (*c* = 0.84, $CHCl_3$); ν_{max} ($CHCl_3$) 2942, 2865, 1731, 1612, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (1H, d, *J* = 2.1 Hz), 7.24 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 5.10 (1H, s), 4.98 (1H, s), 4.41 (2H, s), 4.15 (1H, d, *J* = 12.6 Hz), 3.96 (1H, d, *J* = 12.6 Hz), 3.79 (3H, s), 3.74−3.67 (1H, m), 3.69 (1H, dd, *J* = 9.5, 5.7 Hz), 3.57 (1H, dd, *J* = 9.5, 7.0 Hz), 3.45 (2H, m), 2.39 (1H, qdd, *J* = 7.0, 7.0, 5.7 Hz), 1.81−1.69 (4H, m), 1.09 (3H, d, *J* = 7.0 Hz), 1.07−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 159.2, 148.1, 130.6, 129.3, 113.8, 112.1, 83.2, 73.2, 72.6, 69.4, 68.0, 55.3, 39.4, 26.9, 25.1, 18.1, 16.4, 12.0; HRMS (CI, CH_4) *m*/*z* calcd for $C_{28}H_{48}O_5Si$ $[M]^+$: 492.3271, found: 492.3250 (Δ 4.3 ppm). Anal. calcd for $C_{28}H_{48}O_5Si$: C, 68.25; H, 9.82. Found: C, 67.98; H, 10.10.

(3*R*)-1-Diazo-6-[(4-methoxybenzyl)oxy]-2-{(3*S*)-3-methyl-2-methylene-4-[(triisopropylsilyl)oxy]butoxy}hexan-2-one (15). A solution of sodium chlorite (80%, 9.13 g, 80.8 mmol) and sodium dihydrogenorthophosphate dihydrate (13.63 g, 87.37 mmol) in water (135 mL) was added dropwise over 10 min at room temperature to a solution of the aldehyde **13** (6.63 g, 13.5 mmol) in *t*-butanol (67.5 mL) and 2-methyl-2-butene (90%, 11.40 mL, 107.6 mmol). The mixture was stirred for 90 min at room temperature, and the volatiles were then removed in vacuo. The resulting solution was extracted with ether (3 × 100 mL), and the extracts were combined and washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo. The crude acid **14** was dissolved in dry ether (140 mL) under Ar, and then triethylamine (2.06 mL, 14.8 mmol) and *i*-butyl chloroformate (1.92 mL, 14.8 mmol) were added sequentially. The mixture was stirred for 3 h, then filtered and added dropwise over 1 h to a solution of diazomethane (~150 mmol in 188 mL of ether) at 0 °C. The resulting solution was stirred overnight, and then the excess diazomethane was consumed by the addition acetic acid (10 mL). After 30 min, the solution was diluted with ether (100 mL) and washed with saturated sodium bicarbonate solution (100 mL) and brine (100 mL). The yellow solution was dried ($MgSO_4$) and concentrated in vacuo to afford a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 10:1 to 7:1) gave the α-diazo ketone **15** (6.73 g, 94%) as a yellow oil: R_f = 0.27 (hexane-ethyl acetate, 5:1); $[\alpha]_D^{23}$ +28.6 (*c* = 1.30, $CHCl_3$); ν_{max} ($CHCl_3$) 3124, 2943, 2866, 2109, 1634, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, *J* = 8.7 Hz), 6.87 (2H, d, *J* = 8.7 Hz), 5.73 (1H, br), 5.10 (1H, s), 4.97 (1H, s), 4.42 (2H, s), 4.06 (1H, d, *J* = 12.8 Hz), 3.91 (1H, d, *J* = 12.8 Hz), 3.80 (3H, s), 3.81−3.76 (1H, m), 3.67 (1H, dd, *J* = 9.5, 5.9 Hz), 3.55 (1H, dd, *J* = 9.5, 6.8 Hz), 3.47−3.42 (2H, m), 2.36 (1H, qdd, *J* = 6.8, 6.8, 5.9 Hz), 1.81−1.67 (4H, m), 1.09 (3H, d, *J* = 6.8 Hz), 1.07−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 159.2, 148.1, 130.7, 129.3, 113.8, 111.5, 83.6, 73.0, 72.6, 69.7, 68.1, 55.3, 52.3, 39.6, 30.1, 25.4, 18.1, 16.5, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{49}O_5N_2Si$ $[M + H]^+$: 533.3411, found: 533.3394 (Δ 3.1 ppm). Anal. calcd for $C_{29}H_{48}O_5N_2Si$: C, 65.38; H, 9.08; N, 5.26. Found: C, 65.22; H, 8.98; N, 5.11.

(1*R*,6*S*)-1,4-Anhydro-3,5,6-trideoxy-1-{3-[(4-methoxybenzyl)-oxy]propyl}-6-methyl -2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol (16). A solution of α-diazo ketone **15** (6.60 g, 12.4 mmol) in dry THF (450 mL) was added dropwise over 2 h to a solution of rhodium(II) trifluoroacetamide dimer (30 mg, 0.046 mmol, 0.4 mol %) in dry THF (150 mL) at reflux under N_2. The reaction was stirred at reflux for 10 min, allowed to cool to room temperature, and concentrated in vacuo. The crude dihydrofuranone was dissolved in dry THF (80 mL) and stirred under an atmosphere of Ar. Methylmagnesium chloride (12.4 mL of a 3.0 M solution in THF, 37.2 mmol) was added dropwise over 10 min at −78 °C, and the reaction was stirred overnight under Ar, warming to room temperature during that time. The reaction was cooled to 0 °C and quenched carefully with a saturated solution of ammonium chloride (10 mL). Water (100 mL) was added, and the mixture was extracted with ether (3 × 150 mL). The ether extracts were combined and washed with water (100 mL) and brine (80 mL), then dried ($MgSO_4$) and concentrated in vacuo to deliver a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 3:1) gave the alcohol **16** (3.59 g, 56%) as a colorless oil: R_f = 0.38 (hexane-ethyl acetate, 4:1): $[\alpha]_D^{20}$ −6.7 (*c* = 0.80, $CHCl_3$); ν_{max} ($CHCl_3$) 3553, 2943, 2866, 1613, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (2H, d, *J* = 8.5 Hz), 6.87 (2H, d, *J* = 8.5 Hz), 5.33 (1H, s), 4.89 (1H, s), 4.44 (2H, s), 4.39 (1H, dd, *J* = 9.3, 4.9 Hz), 3.80 (3H, s), 3.66 (1H, dd, *J* = 9.5, 5.6 Hz), 3.56−3.46 (3H, m), 3.45 (1H, dd, *J* = 9.5, 8.0 Hz), 2.21 (1H, dqd, *J* = 8.0, 6.9, 5.6 Hz), 2.21 (1H, dd, *J* = 13.3, 9.3 Hz), 1.93 (1H, dd, *J* = 13.3, 4.9 Hz), 1.93−1.81 (2H, m), 1.77−1.63 (3H, m), 1.25 (3H, s), 1.13 (3H, d, *J* = 6.9 Hz), 1.06−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 154.9, 130.8, 129.3, 113.8, 107.2, 86.7, 78.4, 78.0, 72.6, 70.2, 68.9, 55.3, 46.5, 39.2, 27.1, 25.3, 22.9, 18.1, 17.3, 12.0; HRMS (CI, CH_4) *m*/*z* calcd for $C_{30}H_{52}O_5Si$ $[M]^+$: 520.3584, found: 520.3564 (Δ 3.8 ppm). Anal. calcd for $C_{30}H_{52}O_5Si$: C, 69.18; H, 10.06. Found: C, 68.99; H, 9.94.

(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-{3-[(4-methoxybenzyl)oxy]propyl }-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol (17). Acetic anhydride (2.95 mL, 31.2 mmol) was added to a solution of **16** (4.07 g, 7.81 mmol), DMAP (2.86 g, 23.4 mmol), and Et_3N (8.79 mL, 63.1 mmol) in dry ether (104 mL) at room temperature under Ar, and the resulting solution was stirred for 20 h. Water (300 mL) was added, and the mixture was extracted with ether (3 × 100 mL). The ether extracts were combined and washed with water (100 mL) and brine (50 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 4:1) afforded the acetate **17** (3.94 g, 90%) as a clear oil: R_f = 0.40 (petroleum ether-ethyl acetate, 4:1); $[\alpha]_D^{23}$ −6.8 (*c* = 1.7, $CHCl_3$); ν_{max} ($CHCl_3$) 2942, 2865, 1728, 1612 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (2H, d, *J* = 8.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 5.20 (1H, s), 4.86 (1H, s), 4.47 (1H, d, *J* = 11.6 Hz), 4.43 (1H, d, *J* = 11.6 Hz), 4.31 (1H, dd, *J* = 7.7, 7.5 Hz), 3.80 (3H, s), 3.67 (1H, dd, *J* = 9.5, 5.5 Hz), 3.58−3.46 (3H, m), 3.44 (1H, dd, *J* = 9.5, 7.9 Hz), 2.38 (1H, dd, *J* = 14.0, 7.5 Hz), 2.33 (1H, dd, *J* = 14.0, 7.7 Hz), 2.21−2.17 (1H, dqd, *J* = 7.9, 6.9, 5.5 Hz), 1.94 (3H, s), 1.91−1.88 (1H, m), 1.73−1.65 (3H, m), 1.52 (3H, s), 1.09 (3H, d, *J* = 6.9 Hz), 1.06−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 159.2, 152.4, 130.8, 129.3, 113.8, 108.4, 87.5, 86.1, 79.2, 72.5, 70.1, 68.8, 55.3, 43.7, 38.8, 27.0, 25.9, 22.1, 21.7, 18.1, 17.6, 12.0; HRMS (ES) *m*/*z* calcd for $C_{32}H_{58}O_6NSi$ $[M + NH_4]^+$: 580.4033, found: 580.4044 (Δ 1.9

ppm). Anal. calcd for $C_{32}H_{54}O_6Si$: C, 68.29; H, 9.67. Found: C, 67.93; H, 9.78.

(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(3-hydroxypropyl)-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol (18). DDQ (3.19 g, 14.1 mmol) was added in one portion to a solution of **17** (5.28 g, 9.38 mmol) in CH_2Cl_2 (162 mL) and water (16 mL), and the reaction was stirred at room temperature for 3 h. The reaction was diluted with CH_2Cl_2 (50 mL) and washed successively with a saturated solution of sodium bicarbonate (200 mL), water (150 mL), and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a red−brown oil. Purification by column chromatography (petroleum ether-ethyl acetate, 10:1 to 3:1) gave the alcohol **18** (4.16 g, 100%) as a clear oil: $R_f = 0.08$ (hexane-ethyl acetate, 4:1); $[\alpha]_D^{21}$ −11 ($c = 0.55$, $CHCl_3$); ν_{max} ($CHCl_3$) 3431, 2943, 2866, 1729, 1649, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.19 (1H, s), 4.87 (1H, s), 4.37 (1H, dd, $J = 7.9$, 7.1 Hz), 3.70 (2H, br), 3.64 (1H, dd, $J = 9.4$, 5.8 Hz), 3.51 (1H, dd, $J = 7.0$, 4.5 Hz), 3.45 (1H, dd, $J = 9.4$, 8.0 Hz), 2.52 (1H, br), 2.45 (1H, dd, $J = 14.1$, 7.1 Hz), 2.33 (1H, dd, $J = 14.1$, 7.9 Hz), 2.18 (1H, dqd, $J = 8.0$, 7.0, 5.8 Hz), 1.94 (3H, s), 1.80−1.76 (4H, m), 1.53 (3H, s), 1.08 (3H, d, $J = 7.0$ Hz), 1.06−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 152.2, 108.5, 87.9, 86.1, 79.4, 68.9, 63.0, 43.3, 38.7, 30.5, 26.1, 22.1, 21.5, 18.1, 17.5, 12.0; HRMS (ES) *m*/*z* calcd for $C_{24}H_{46}O_5SiNa$ $[M + Na]^+$: 465.3012, found: 465.3017 (Δ 1.0 ppm). Anal. calcd for $C_{24}H_{46}O_5Si$: C, 65.11; H, 10.47. Found: C, 65.14; H, 10.68.

(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(3-oxopropyl)-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol (19). Dess−Martin periodinane (8.27 g, 19.5 mmol) was added in three portions at 30 min intervals to a solution of the alcohol **18** (5.77 g, 13.0 mmol) in dry CH_2Cl_2 (63 mL) at 0 °C under Ar. The mixture was stirred for a further 2 h at room temperature, then quenched by the addition of a saturated solution of sodium thiosulfate (150 mL) and extracted with ether (3 × 100 mL). The ether extracts were combined and washed successively with a saturated solution of sodium bicarbonate (150 mL), water (100 mL), and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a cloudy oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 3:1) gave the aldehyde **19** (5.34 g, 93%) as a clear oil: $R_f = 0.60$ (hexane-ethyl acetate, 4:1); $[\alpha]_D^{23}$ −3.8 ($c = 0.90$, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2892, 2866, 2728, 1727, 1649, 1602, 1649, 906, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.83 (1H, t, $J = 1.3$ Hz), 5.16 (1H, t, $J = 1.3$ Hz), 4.86 (1H, s), 4.33 (1H, t, $J = 7.6$ Hz), 3.64 (1H, dd, $J = 9.5$, 5.7 Hz), 3.51 (1H, dd, $J = 9.2$, 3.6 Hz), 3.45 (1H, dd, $J = 9.5$, 7.7 Hz), 2.73 (1H, dddd, $J = 18.1$, 8.0, 6.2, 1.3 Hz), 2.62 (1H, dddd, $J = 18.1$, 8.0, 6.9, 1.3 Hz), 2.39−2.36 (2H, m), 2.18 (1H, dqd, $J = 7.7$, 6.9, 5.7 Hz), 2.01−1.94 (2H, m), 1.96 (3H, s), 1.55 (3H, s), 1.08 (3H, d, $J = 6.9$ Hz), 1.06−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.3, 170.3, 152.2, 108.5, 86.5, 86.0, 79.4, 68.8, 43.6, 41.2, 38.7, 22.1, 21.8, 21.6, 18.1, 17.5, 12.0; HRMS (CI, NH_3) *m*/*z* calcd for $C_{24}H_{45}O_5Si$ $[M + H]^+$: 441.3036, found: 441.3028 (Δ 1.8 ppm).

(1*R*,6*S*)-2-*O*-Acetyl-1,4-anhydro-3,5,6-trideoxy-1-(4-diazo-3-oxobutyl)-6-methyl-2-*C*-methyl-5-methylene-7-*O*-(triisopropylsilyl)-D-*xylo*-heptitol (21). A solution of sodium chlorite (80%, 5.48 g, 48.5 mmol) and sodium dihydrogenorthophosphate dihydrate (8.18 g, 52.5 mmol) in water (81 mL) was added dropwise over 10 min to a solution of the aldehyde **19** (3.56 g, 8.08 mmol) in *t*-butanol (41 mL) and 2-methyl-2-butene (6.85 mL, 64.6 mmol). The reaction was stirred at room temperature for 90 min, and then the volatile compounds were removed in vacuo. The mixture was extracted with ether (3 × 100 mL), and the ether extracts were combined and washed with water (100 mL) and brine (10 mL) and then dried ($MgSO_4$) and concentrated in vacuo to give the carboxylic acid **20** as a pale yellow oil. The crude acid **20** was dissolved in dry MeOH (89 mL) under Ar, and sodium methoxide (458 mg, 8.48 mmol) was added in one portion. The mixture was stirred for 15 min, concentrated in vacuo, and dried for 1 h under high vacuum. The white solid was dissolved in dry benzene (89 mL), and oxalyl chloride (3.52 mL, 40.4 mmol) was added dropwise over 10 min at room temperature under Ar. The mixture was stirred for 2 h and concentrated in vacuo, and the residue was dissolved in CH_2Cl_2 (75 mL). The solution was then added dropwise over 30 min to a solution of diazomethane (∼40 mmol in 55 mL of ether) at 0 °C. The resulting mixture was stirred for 2 h, and then the excess diazomethane was consumed by the addition of acetic acid (5 mL). After 30 min, the ethereal solution was diluted with ether (200 mL) and washed with a saturated solution of sodium bicarbonate (150 mL). The aqueous layer was separated and extracted with ether (2 × 50 mL). The ether extracts were combined and washed with water (100 mL) and brine (100 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Purification by column chromatography (petroleum ether-ethyl acetate, 9:1 to 4:1) gave the α-diazo ketone **21** (2.91 g, 75%) as a yellow oil: $R_f = 0.25$ (hexane-ethyl acetate, 4:1); $[\alpha]_D^{23}$ −0.98 ($c = 0.62$, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2891, 2866, 2109, 1729, 1640, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.30 (1H, br) 5.18 (1H, s), 4.86 (1H, s), 4.33 (1H, dd, $J = 7.8$, 7.5 Hz), 3.65 (1H, dd, $J = 9.5$, 5.7 Hz), 3.51 (1H, dd, $J = 9.3$, 3.5 Hz), 3.45 (1H, dd, $J = 9.5$, 7.8 Hz), 2.61 (1H, br), 2.49 (1H, br), 2.40 (1H, dd, $J = 14.0$, 7.5 Hz), 2.36 (1H, dd, $J = 14.0$, 7.8 Hz), 2.18 (1H, dqd, $J = 7.8$, 6.9, 5.7 Hz), 2.02−1.95 (2H, m), 1.96 (3H, s), 1.54 (3H, s), 1.09 (3H, d, $J = 6.9$ Hz), 1.02−1.06 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 170.4, 152.4, 108.4, 86.5, 86.0, 79.4, 68.8, 54.6, 43.5, 38.8, 37.8, 24.4, 22.1. 21.6, 18.1, 17.6, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{45}N_2O_5Si$ $[M + H]^+$: 481.3098, found: 481.3132 (Δ 7.1 ppm). Anal. calcd for $C_{25}H_{44}N_2O_5Si$: C, 62.46; H, 9.23; N, 5.83. Found: C, 62.82; H, 9.36; N, 5.48.

(1*R*,2*R*,4*Z*,7*R*)-2-Methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-8-oxo-11-oxabicyclo[5.3.1]undec-4-en-2-yl Acetate (23) and (1*R*,2*R*,4*R*,5*R*)-2-Methyl-4-{(2*S*)-2-methyl-1-methylene-3-[(triisopropylsilyl)oxy]propyl}-6-oxo-9-oxabicyclo[3.3.1]non-2-yl Acetate (24). A solution of the α-diazo ketone **21** (2.86 g, 5.95 mmol) in dry CH_2Cl_2 (357 mL) was added dropwise over 1 h to a solution of copper(II) hexafluoroacetylacetonate (65 mg, 0.13 mmol, 2.2 mol %) in dry CH_2Cl_2 (89 mL) at reflux under N_2. The reaction was stirred at reflux for 5 min, cooled to room temperature, and concentrated in vacuo to a green oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 7:3) gave the [2,3] rearrangement product **23** (1.86 g, 69%, 2:3 mixture of *E*/*Z* isomers) as a white solid and the [1,2] shift product **23** (435 mg, 16%) as a colorless oil.

AIBN (415 mg, 2.53 mmol) was added in four portions, over 4 h, to a solution of ketone **23** (2.29 g of a 3:2 *Z*/*E* isomer mixture, 5.06 mmol) and ethanethiol (18 mL) in dry benzene (226 mL) at reflux under Ar. The solution was then cooled and concentrated in vacuo to yield a yellow oil. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 19:1 to 9:1) afforded the alkene ***Z*-23** (2.28 g, >99%) as a white solid.

***Z*-23**: mp 50−53 °C; $R_f = 0.38$ (hexane-ethyl acetate, 4:1); $[\alpha]_D^{23}$ +57 ($c = 1.3$, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2892, 2866, 1724, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.61 (1H, t, $J = 8.3$ Hz), 4.42 (1H, t, $J = 9.3$ Hz), 4.05−4.02 (1H, br), 3.64 (1H, dd, $J = 9.7$, 5.9 Hz), 3.49 (1H, dd, $J = 9.7$, 6.7 Hz), 2.59−2.44 (4H, m), 2.42−2.35 (1H, m), 2.34−2.26 (2H, m), 2.19−2.09 (2H, m), 1.98 (3H, s), 1.72 (3H, s), 1.08−1.02 (24H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.0, 170.0, 140.9, 123.4, 87.3, 79.6, 77.3, 67.7, 43.3, 35.4, 34.5, 32.2, 22.4, 22.4, 20.1, 18.1, 16.3, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{45}O_5Si$ $[M + H]^+$: 453.3036, found: 453.3017 (Δ 4.3 ppm). Anal. calcd for $C_{25}H_{44}O_5Si$: C, 66.33; H, 9.80. Found: C, 66.14; H, 9.85.

24: $R_f = 0.4$ (hexane-ethyl acetate, 4:1); $[\alpha]_D^{21}$ −7.1 ($c = 1.1$, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2892, 2866, 1729, 1643, 901, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84 (1H, s), 4.67 (1H, s), 4.51−4.47 (1H, m), 4.16 (1H, d, $J = 5.6$ Hz), 3.89 (1H, dd, $J = 9.5$, 4.5 Hz), 3.52 (1H, dd, $J = 9.5$, 8.9 Hz), 2.83−2.75 (1H, m), 2.64−2.55 (1H, m), 2.35−2.18 (3H, m), 2.13 (1H, dd, $J = 13.7$,

3.7 Hz), 2.10−2.05 (1H, m), 2.01 (3H, s), 1.85 (1H, t, J = 13.7 Hz), 1.78 (3H, s), 1.13 (3H, d, J = 6.8 Hz), 1.12−1.02 (21H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.4, 169.9, 149.8, 110.2, 81.0, 79.2, 71.3, 67.3, 41.6, 41.4, 35.7, 34.3, 22.9, 22.2, 21.7, 18.6, 18.1, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{45}O_5Si$ $[M + H]^+$: 453.3036, found: 453.2993 (Δ 9.6 ppm). Anal. calcd for $C_{25}H_{44}O_5Si$: C, 66.33; H, 9.80. Found C, 65.96; H, 9.65.

(1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-3-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-11-oxo-4,12-dioxatricyclo[6.3.1.0^{3,5}]dodec-7-yl Acetate (25). Purified *m*-CPBA (211 mg, 1.22 mmol) (***Caution!*** *Explosion hazard.*) was added to a solution of the alkene **23** (369 mg, 0.815 mmol) in dry CH_2Cl_2 (40 mL) under N_2.[46] The reaction mixture was heated at reflux for 1 h and then allowed to cool to room temperature. The reaction was quenched by the addition of a saturated solution of sodium thiosulfate (20 mL), and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The organic extracts were combined and washed with a saturated solution of sodium bicarbonate (20 mL), water (20 mL), and brine (20 mL), then dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography (hexane-ethyl acetate, 9:1 to 4:1) gave the epoxide **25** (305 mg, 80%, 22:1 mixture of diastereoisomers) as a white solid: mp 83−85 °C; R_f = 0.37 (hexane-ethyl acetate, 4:1); $[\alpha]_D^{23}$ −6.5 (c = 0.46, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2866, 1730, 882 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.46 (1H, dd, J = 12.3, 6.1 Hz), 4.25 (1H, dd, J = 13.9, 5.0 Hz), 3.83 (1H, dd, J = 9.8, 5.8 Hz), 3.51 (1H, dd, J = 9.8, 6.7 Hz), 3.12 (1H, dd, J = 9.8, 5.3 Hz), 2.74 (1H, dd, J = 14.2, 5.3 Hz), 2.63 (1H, dd, J = 14.4, 5.0 Hz), 2.60−2.46 (2H, m), 2.17−2.08 (1H, m), 1.99 (3H, s), 1.96−1.84 (2H, m), 1.82 (3H, s), 1.66 (1H, dd, J = 14.2, 10.0 Hz), 1.31 (1H, dd, J = 14.4, 13.9 Hz), 1.12−1.04 (21H, m), 0.90 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$), δ 210.7, 170.0, 82.9, 76.8, 76.5, 65.6, 62.4, 56.8, 39.0, 36.8, 35.2, 33.4, 22.5, 22.1, 19.9, 18.1, 13.0, 11.9; HRMS (FAB) *m*/*z* calcd for $C_{25}H_{45}O_6Si$ $[M + H]^+$: 469.2985, found: 469.2980 (Δ 1.1 ppm). Anal. calcd for $C_{25}H_{44}O_6Si$: C, 64.06; H, 9.46. Found: C, 63.84; H, 9.24.

(1*R*,3*S*,5*S*,7*R*,8*R*)-7-Methyl-11-methylene-3-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-4,12-dioxatricyclo[6.3.1.0^{3,5}]dodec-7-yl acetate (26). Using the Nysted reagent.[25] Titanium(IV) chloride (1.60 mL of a 1 M solution in CH_2Cl_2, 1.60 mmol) was added to a solution of Nysted reagent {cyclo-dibromodi-μ-methylene-[μ-(tetrahydrofuran)]trizinc} (3.86 mL of a 20 wt % suspension in THF, 2.01 mmol) in THF (6 mL) at 0 °C under N_2. After the mixture was stirred for 5 min, a solution of the ketone **25** (376 mg, 0.802 mmol) in THF (14 mL) was added at 0 °C under N_2. The reaction was stirred for 90 min and warmed to room temperature during this period. The reaction was then quenched by the addition of 0.5 N HCl (20 mL), and the reaction mixture was extracted with ether (3 × 20 mL). The ether extracts were combined and washed with water (25 mL) and brine (20 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 19:1 to 4:1) afforded the alkene **26** (332 mg, 89%) as a colorless oil.

Using the Petasis protocol.[24] Dimethyltitanocene (493 mg, 2.37 mmol) and the ketone **25** (370 mg, 0.789 mmol) were dissolved in dry THF (40 mL) under Ar, and the resulting orange solution was heated at reflux for 20 h. The mixture was cooled to room temperature, and a saturated solution of sodium bicarbonate (30 mL) was added. The mixture was extracted with ether (3 × 40 mL), and the ether extracts were combined and washed with water (40 mL) and brine (40 mL), then dried ($MgSO_4$) and concentrated in vacuo to an orange oil. The crude product was dry-loaded onto silica gel and purified by column chromatography on silica gel (petroleum ether-ethyl acetate, 9:1 to 4:1) to give the alkene **26** (298 mg, 81%) as a colorless oil.

R_f = 0.51 (hexane-ethyl acetate, 4:1); $[\alpha]_D^{25}$ −6.6 (c = 1.4, $CHCl_3$); ν_{max} ($CHCl_3$) 2943, 2866, 1728, 1646, 1602, 884 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.81 (1H, s), 4.67 (1H, s), 4.54 (1H, dd, J = 13.2, 4.8 Hz), 4.20 (1H, dd, J = 12.2, 6.0 Hz,), 3.88 (1H, dd, J = 9.8, 5.6 Hz), 3.50 (1H, dd, J = 9.8, 7.1 Hz), 3.09 (1H, dd, J = 9.8, 5.3 Hz), 2.71 (1H, dd, J = 13.9, 5.3 Hz), 2.55−2.48 (1H, m), 2.39 (1H, dd, J = 14.7, 4.8 Hz), 2.35−2.28 (1H, m), 2.05 (1H, dqd, J = 7.1, 7.0, 5.6 Hz), 1.96 (3H, s), 1.85−1.78 (1H, m), 1.77 (3H, s), 1.68 (1H, dd, J = 13.9, 9.8 Hz), 1.64−1.56 (1H, m), 1.40 (1H, dd, J = 14.7, 13.2 Hz), 1.08−1.04 (21H, m), 0.92 (3H, d, J = 7.0 Hz); ^{13}C NMR (100 Hz, $CDCl_3$) δ 170.0, 147.2, 107.4, 83.4, 77.3, 72.6, 65.9, 62.8, 56.9, 43.3, 38.6, 33.5, 26.8, 22.5, 22.1, 20.8, 18.1, 13.1, 12.0; HRMS (FAB) *m*/*z* calcd for $C_{26}H_{47}O_5Si$ $[M + H]^+$: 467.3193, found: 467.3193 (Δ 0 ppm). Anal. calcd for $C_{26}H_{46}O_5Si$: C, 66.91; H, 9.93. Found: C, 66.98; H, 9.92.

(1*R*,2*R*,4*S*,5*Z*,7*R*)-2-Methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-11-oxabicyclo[5.3.1]undec-5-ene-2,4-diol (27) and (1*R*,6*R*)-1,5-Anhydro-3,6-dideoxy-6-methyl-2-*C*-methyl-1-(3-methylenepent-4-en-1-yl)-7-*O*-(triisopropylsilyl)-D-*erythro*-heptitol (28). Aluminum isopropoxide (490 mg, 2.40 mmol) was added to a solution of the epoxide **26** (112 mg, 0.240 mmol) in dry toluene (15 mL) at room temperature under N_2. The reaction mixture was heated at reflux for 18 h and then allowed to cool to room temperature. The reaction mixture was concentrated in vacuo to ∼10% volume and diluted with ether (20 mL). A 0.5 M solution of HCl (15 mL) was added, and the mixture was extracted with ether (3 × 15 mL). The ether extracts were combined and washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 3:1 to 2:1) gave the diol **27** (61 mg, 60%) and the diene **28** (40 mg, 39%, 5.5:1 mixture of diastereoisomers) as colorless oils.

27: R_f = 0.21 (hexane-ethyl acetate, 3:1); $[\alpha]_D^{24}$ −31 (c = 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3382, 2945, 2868, 1656, 1601, 907, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.51 (1H, ddt, J = 9.3, 4.0, 2.0 Hz), 5.21 (1H, dd, J = 2.0, 1.1 Hz), 4.81 (1H, s), 4.79 (2H, s), 4.13 (1H, s, O*H*), 3.80 (1H, dd, J = 8.4, 4.5 Hz), 3.70 (1H, dd, J = 7.2, 6.4 Hz), 3.30 (1H, dd, J = 10.5, 8.4 Hz), 3.17 (1H, dqd, J = 10.5, 7.1, 4.5 Hz), 2.71−2.62 (1H, m), 2.30−2.18 (2H, m), 2.08−2.07 (1H, dd, J = 14.0, 4.0 Hz), 2.04−1.95 (1H, m), 1.96 (1H, dd, J = 14.0, 9.3 Hz), 1.89−1.80 (1H, m), 1.35 (3H, s, CC*H*$_3$), 1.10−1.04 (21H, m), 1.00 (3H, d, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 146.9, 126.7, 108.4, 80.1, 76.2, 74.9, 71.7, 66.6, 48.3, 33.2, 28.4, 26.2, 22.9, 17.9, 17.6, 11.9; HRMS (ESI) *m*/*z* calcd for $C_{24}H_{44}O_4SiNa$ $[M + Na]^+$: 447.2907, found: 447.2884 (Δ 2.3 ppm).

28 (5.5:1 mixture of diastereoisomers): R_f = 0.46 (hexane-ethyl acetate, 3:1); $[\alpha]_D^{24}$ +19 (c = 0.45, $CHCl_3$); ν_{max} ($CHCl_3$) 3422, 2944, 2867, 1595, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.39 (1H, dd, J = 17.7, 10.9 Hz, minor), 6.38 (1H, dd, J = 17.6, 11.0 Hz, major), 5.27 (1H, ddt, J = 17.6, 1.1, 0.5 Hz, major), 5.26 (1H, ddt, J = 17.8, 1.1, 0.5 Hz, minor), 5.07−5.03 (3H, m), 4.14 (1H, ddd, J = 10.2, 3.3, 1.8 Hz, minor), 4.05 (1H, ddd, J = 9.6, 3.5, 2.5 Hz, major), 4.02 (1H, dd, J = 3.9, 2.5 Hz, minor), 3.85 (1H, dd, J = 9.8, 3.7 Hz, major), 3.74 (1H, dd, J = 9.5, 4.1 Hz, minor), 3.72 (1H, dd, J = 9.8, 5.1 Hz major), 3.46 (1H, dd, J = 9.4, 2.9 Hz, minor), 3.37 (1H, dd, J = 9.2, 3.0 Hz, major), 2.48 (1H, ddd, J = 14.6, 10.4, 4.9 Hz), 2.30−2.23 (1H, m), 2.23−2.21 (1H, m, minor), 2.20 (1H, dd, J = 13.6, 3.5 Hz, major), 2.10−2.07 (1H, m, minor), 2.05 (1H, dd, J = 13.6, 9.6 Hz, major), 1.98 (1H, dd, J = 13.6, 3.3 Hz, minor), 1.86−1.78 (2H, m), 1.77−1.68 (1H, m), 1.26 (3H, s, major), 1.24 (3H, s, minor), 1.12−1.04 (21H, m), 1.01 (3H, d, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 139.1, 115.7, 113.3, 85.7, 78.2, 76.9, 69.0, 41.9, 37.7, 28.4, 26.6, 22.2, 18.1, 12.2, 11.9; HRMS (CI, CH_4) *m*/*z* calcd for $C_{24}H_{47}O_4Si$ $[M + H]^+$: 427.3244, found: 427.3256 (Δ 2.9 ppm).

(46) Commercial *m*-chloroperbenzoic acid was purified according to the the procedure described in: Armarego, W. L. F.; Perkin, D. D. *Purification of Laboratory Chemicals*, 4th ed.; 1996; p 145. A solution of *m*-chloroperbenzoic acid in benzene was washed with aqueous pH 7.4 buffer, and the solution was dried ($MgSO_4$). The solvent was removed at water pump pressure on a rotary evaporator behind a blast screen. The solid *m*-chloroperbenzoic acid was used without recrystallization.

(1*R*,2*R*,4*S*,5*Z*,7*R*)-2-Methyl-8-methylene-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis(triethylsilyloxy)-11-oxabicyclo-[5.3.1]undec-5-ene (29). Triethylsilyl trifluoromethanesulfonate (183 μL, 0.809 mmol) was added dropwise over 2 min to a solution of the diol **27** (72 mg, 0.17 mmol) and 2,6-lutidine (296 μL, 2.54 mmol) in dry CH_2Cl_2 (4 mL) at −78 °C under Ar. The mixture was stirred at −78 °C for 30 min, and the reaction was then quenched by the addition of water (3 mL) and a saturated solution of copper sulfate (3 mL). The mixture was extracted with ether (3 × 5 mL), and the combined ether extracts were washed with water (5 mL) and brine (5 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 19:1 to 9:1) gave the diene **29** (108 mg, 98%) as a colorless oil: $R_f = 0.72$ (hexane-ethyl acetate, 3:1); $[\alpha]_D^{24}$ +26 ($c = 0.30$, $CHCl_3$); ν_{max} 2955, 2874, 1601, 882 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, d, $J = 9.3$ Hz), 5.05 (1H, s), 4.78 (2H, s), 4.76 (1H, s), 3.73 (1H, dd, $J = 9.2$, 4.7 Hz), 3.51 (1H, dd, $J = 12.7$, 4.2 Hz), 3.44 (1H, dd, $J = 9.2$, 7.4 Hz), 2.88 (1H, dqd, $J = 7.4$, 7.0, 4.7 Hz), 2.64 (1H, br d, $J = 16.1$ Hz), 2.34 (1H, dd, $J = 13.9$, 9.3 Hz), 2.32−2.20 (1H, m), 1.92 (1H, dddd, $J = 13.8$, 13.2, 12.7, 4.5), 1.85−1.77 (1H, m), 1.72 (1H, d, $J = 13.9$ Hz), 1.51 (3H, s), 1.16 (3H, d, $J = 7.0$ Hz), 1.09−1.04 (21H, m), 0.98 (9H, t, $J = 8.0$ Hz), 0.94 (9H, t, $J = 7.8$ Hz), 0.62 (6H, q, $J = 7.8$ Hz) 0.58 (6H, q, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 145.9, 127.5, 108.1, 83.0, 76.1, 75.5, 68.1, 66.8, 50.4, 35.3, 27.9, 25.8, 20.9, 19.6, 18.2, 12.1, 7.2, 7.0, 7.0, 5.1; HRMS (FAB) *m/z* calcd for $C_{36}H_{72}O_4Si_3$ $[M]^+$: 652.4738, found: 652.4709 (Δ 4.6 ppm). Anal. calcd for $C_{36}H_{72}O_4Si_3$: C, 66.19; H, 11.11. Found C, 66.14; H, 11.21.

(1*R*,2*R*,4*S*,5*Z*,7*R*,8*R*)-8-(Hydroxymethyl)-2-methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis[(triethylsilyl)oxy]-11-oxabicyclo[5.3.1]undec-5-en-8-ol (30). A solution of osmium tetroxide (4% in H_2O, 42 μL, 5 mol %) was added to a solution of the alkene **29** (89 mg, 0.14 mmol) and NMO (48 mg, 0.41 mmol) in acetone (3 mL) and water (0.5 mL) at room temperature. The reaction mixture was allowed to stir at room temperature for 24 h. TLC analysis revealed that the reaction was incomplete, so additional osmium tetroxide (4% in H_2O, 42 μL, 5 mol %) was added, and the reaction was allowed to stir at room temperature for a further 24 h. The reaction was quenched with sodium metabisulfite (500 mg), diluted with water (5 mL), and extracted with ether (3 × 10 mL). The ether extracts were combined and washed with water (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 9:1 to 4:1) gave the diol **30** (75 mg, 80%) as a colorless oil: $R_f = 0.28$ (hexane-ethyl acetate, 3:1); $[\alpha]_D^{25}$ +2.3 ($c = 1.13$, $CHCl_3$). ν_{max} ($CHCl_3$) 3572, 2955, 2874, 1602, 883 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.40 (1H, d, $J = 9.7$ Hz), 5.29 (1H, s), 4.33 (1H, s), 3.75 (1H, dd, $J = 9.3$, 4.6, Hz), 3.64 (1H, dd, $J = 13.1$, 5.1 Hz), 3.60 (2H, d, $J = 6.1$ Hz), 3.43 (1H, dd, $J = 9.3$, 7.4 Hz), 3.11 (1H, br), 2.90 (1H, dqd, $J = 7.4$, 7.0, 4.6 Hz), 2.31 (1H, dd, $J = 13.9$, 9.7 Hz), 2.24 (1H, t, $J = 6.1$ Hz), 1.95−1.83 (1H, m), 1.78−1.66 (3H, m), 1.55 (3H, s), 1.58−1.53 (1H, m), 1.16 (3H, d, $J = 7.0$ Hz), 1.09−1.04 (21H, m), 0.96 (9H, t, $J = 8.0$ Hz), 0.93 (9H, t, $J = 7.9$ Hz), 0.61 (6H, q, $J = 7.9$ Hz), 0.56 (6H, q, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 120.2, 80.5, 75.6, 74.7, 73.8, 68.2, 67.0, 66.8, 49.5, 35.6, 28.4, 28.1, 19.6, 19.0, 18.1, 12.1, 7.1, 7.0, 6.9, 5.0; HRMS (FAB) calcd for $C_{36}H_{74}O_6Si_3$ $[M^+]$: 686.4793, found: 686.4789 (Δ 0.6 ppm). Anal. calcd for $C_{36}H_{74}O_6Si_3$: C, 62.92; H, 10.85. Found C, 62.61; H, 10.61.

Methyl (1*R*,2*R*,4*S*,5*Z*,7*R*,8*S*)-8-Hydroxy-2-methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis[(triethylsilyl)-oxy]-11-oxabicyclo[5.3.1]undec-5-ene-8-carboxylate (33) and (1*R*,2*R*,4*S*,5*Z*,7*R*,1′*S*)-2-Methyl-5-{(1*S*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis[(triethylsilyl)oxy]-11-oxabicyclo[5.3.1]-undec-5-en-8-one (34). A saturated solution of sodium bicarbonate (216 μL) containing tetra-*n*-butylammonium bromide (1.8 mg, 5 mol %) was added to a solution of the alcohol **30** (75 mg, 0.11 mmol) and TEMPO (0.9 mg, 5 mol %) in CH_2Cl_2 (2.4 mL) at room temperature. The solution was cooled to 0 °C, and a solution of sodium hypochlorite (0.218 mmol) in a saturated solution of sodium bicarbonate (115 μL) and brine (238 μL) was added over 5 min. The reaction was stirred at 0 °C for 15 min and then quenched with water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give the aldehyde **31** as a clear oil. The aldehyde **31** was dissolved in a mixture of *t*-butanol (545 μL) and 2-methyl-2-butene (93 μL, 0.88 mmol) at room temperature. A solution of sodium chlorite (80%, 74 mg, 0.82 mmol) and sodium dihydrogenorthophosphate dihydrate (111 mg, 0.712 mmol) in water (1.1 mL) was added dropwise to this mixture over 5 min at room temperature. The mixture was stirred at room temperature for 15 min and then diluted with CH_2Cl_2 (10 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic extracts were then dried ($MgSO_4$) and concentrated in vacuo to give the acid **32** as a yellow oil. The crude acid **32** was dissolved in dry CH_2Cl_2 (5 mL) under Ar, and a solution of trimethylsilyldiazomethane (2.0 M in ether, 273 μL, 0.546 mmol) was added dropwise over 2 min at 0 °C. The reaction was allowed to stir for 20 min at 0 °C and then quenched by the addition of a saturated solution of ammonium chloride (5 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Purification by column chromatography (hexane-ethyl acetate, 19:1 to 4:1) afforded the methyl ester **33** (20 mg, 26%) and the ketone **34** (34 mg, 48%) as colorless oils.

33: $R_f = 0.45$ (hexane-ethyl acetate, 3:1); $[\alpha]_D^{28}$ −4.0 ($c = 0.50$, $CHCl_3$); ν_{max} ($CHCl_3$) 2927, 2867, 1724, 883 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.36 (1H, d, $J = 9.6$ Hz), 5.09 (1H, s), 4.30 (1H, s), 3.81 (3H, s), 3.70 (1H, dd, $J = 9.2$, 4.7 Hz), 3.65 (1H, dd, $J = 13.2$, 5.1, Hz), 3.36 (1H, dd, $J = 9.2$, 7.6 Hz), 3.04 (1H, s), 2.89 (1H, dqd, $J = 7.6$, 7.0, 4.7 Hz), 2.73 (1H, dd, $J = 14.7$, 6.8 Hz), 2.30 (1H, dd, $J = 14.1$, 9.6 Hz), 1.94−1.86 (1H, m), 1.81−1.73 (1H, m), 1.69 (1H, d, $J = 14.1$ Hz), 1.65−1.59 (1H, m), 1.55 (3H, s), 1.15 (3H, d, $J = 7.0$ Hz), 1.06−1.03 (21H, m), 0.95 (9H, t, $J = 7.9$ Hz), 0.92 (9H, t, $J = 7.9$ Hz), 0.60 (6H, q, $J = 7.9$ Hz), 0.54 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 148.4, 120.0, 80.5, 76.2, 75.5, 68.1, 67.1, 52.9, 49.6, 35.6, 28.0, 27.3, 19.4, 18.7, 18.1, 12.2, 7.1, 7.0, 7.0, 5.1; LRMS (CI, CH_4) *m/z* 715 (M^+, 8.6%), 655 (4.6%), 542 (79.0%).

34: $R_f = 0.87$ (hexane-ethyl acetate, 19:1); $[\alpha]_D^{18}$ +62 ($c = 0.28$, $CHCl_3$); ν_{max} ($CHCl_3$) 2957, 2875, 1723, 881 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (1H, d, $J = 8.9$ Hz), 4.95 (1H, s), 4.62 (1H, s), 3.71 (1H, dd, $J = 9.3$, 4.7 Hz), 3.68 (1H, dd, $J = 9.8$, 5.7 Hz), 3.43 (1H, dd, $J = 9.3$, 7.6 Hz), 2.88 (1H, dqd, $J = 7.6$, 6.9, 4.7 Hz), 2.59 (1H, dt, $J = 18.4$, 2.7 Hz), 2.38−2.28 (2H, m), 2.17−2.12 (1H, m), 2.03−1.91 (1H, m), 1.78 (1H, d, $J = 14.2$ Hz), 1.58 (3H, s), 1.13 (3H, d, $J = 6.9$ Hz), 1.06−1.03 (21H, m), 0.96 (9H, t, $J = 7.9$ Hz), 0.94 (9H, t, $J = 7.9$ Hz), 0.61 (6H, q, $J = 7.9$ Hz), 0.58 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.4, 149.6, 119.4, 82.8, 80.2, 75.3, 67.7, 66.6, 50.7, 36.1, 36.0, 27.8, 20.6, 19.7, 18.1, 12.1, 7.1, 7.0, 7.0, 5.1.

Methyl (1*R*,2*R*,4*S*,5*S*,6*S*,7*R*,8*S*)-5,6,8-Trihydroxy-2-methyl-5-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-2,4-bis[(triethylsilyl)oxy]-11-oxabicyclo[5.3.1]undecane-8 -carboxylate (35). Osmium tetroxide (4% in water, 341 μL, 0.0536 mmol) was added to a solution of the alkene **33** (40 mg, 0.056 mmol) and NMO (20 mg, 0.17 mmol) in acetone (2 mL), water (0.4 mL), and pyridine (14 μL, 0.17 mmol) at room temperature. The reaction was stirred at room temperature for 3 h, then quenched by the addition of solid sodium metabisulfite (200 mg). The reaction mixture was diluted with water (10 mL) and ether (10 mL), and the aqueous layer was then removed and extracted with ether (2 × 10 mL). The ether extracts were combined and washed with a saturated solution of sodium thiosulfate (10 mL) and a saturated solution of copper sulfate (10 mL) and brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo to give a brown oil. Purification by column

chromatography (hexane-ethyl acetate, 1:1) gave the triol ester **35** (35 mg, 84%) as an oil: $R_f = 0.16$ (petroleum ether-ethyl acetate, 3:1); $[\alpha]_D^{19}$ +230 ($c = 0.50$, $CHCl_3$); ν_{max} ($CHCl_3$) 2956, 2873, 1722, 1608, 872, 832 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.88 (1H, d, $J = 5.9$ Hz), 4.46 (1H, d, $J = 10.1$ Hz), 4.36 (1H, d, $J = 10.1$ Hz), 4.29 (1H, dd, $J = 9.7$, 6.4 Hz), 3.78 (1H, dd, $J = 9.7$, 8.1 Hz), 3.72 (1H, dd, $J = 10.1$, 7.3 Hz), 3.40 (1H, br), 3.35 (3H, s), 2.78−2.68 (3H, m), 1.88−1.80 (2H, m), 1.78 (1H, d, $J = 15.1$ Hz), 1.67−1.58 (1H, m), 1.55 (3H, s), 1.17 (3H, d, $J = 7.1$ Hz), 1.15−1.11 (21H, m), 0.97 (9H, t, $J = 7.9$ Hz), 0.77 (9H, t, $J = 7.9$ Hz), 0.60 (6H, q, $J = 7.9$ Hz), 0.56−0.39 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.1, 98.2, 89.5, 80.7, 77.9, 75.5, 75.0, 73.6, 66.7, 52.5, 47.3, 42.9, 29.7, 27.0, 19.2, 18.3, 14.9, 12.4, 7.2, 7.1, 7.0, 5.5.

(1*R*,2*S*,4*S*,5*S*,7*R*,8*R*,11*R*)-11-(Hydroxymethyl)-7-methyl-4-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-5,7-bis[(triethylsilyl)oxy)]-3,12-dioxatricyclo[6.3.1.0^{2,4}]dodecan-11-ol (38). *m*-CPBA (50−55%, 66 mg, 0.19 mmol) was added to a solution of the alkene **30** (87 mg, 0.13 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C under Ar. The reaction vessel was then removed from the ice bath and the mixture was stirred for 4 h. The reaction was quenched by the addition of a saturated solution of sodium thiosulfate (10 mL), and the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL). The organic extracts were combined and washed with a saturated solution of sodium bicarbonate (10 mL), water (10 mL), and brine (10 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography (isohexane-ethyl acetate, 9:1 to 4:1) gave the epoxide **38** (76.5 mg, 86%) as a colorless, viscous oil: $R_f = 0.29$ (isohexane-ethyl acetate, 4:1). $[\alpha]_D^{18}$ +54 ($c = 0.98$, $CHCl_3$); ν_{max} ($CHCl_3$) 3568, 2955, 2874, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.24 (1H, d, $J = 9.9$ Hz), 4.01 (1H, s), 3.83 (1H, dd, $J = 9.6$, 4.5 Hz), 3.66 (2H, s), 3.61 (1H, dd, $J = 12.4$, 4.0 Hz), 3.32 (1H, dd, $J = 9.6$, 8.0 Hz), 3.00 (1H, s), 2.98 (1H, br), 2.65 (1H, dqd, $J = 8.0$, 7.0, 4.5 Hz), 2.45 (1H, dd, $J = 14.6$, 9.9 Hz), 2.21 (1H, br), 1.95−1.88 (1H, m), 1.84−1.50 (3H, m), 1.60 (1H, d, $J = 14.6$ Hz), 1.46 (3H, s), 1.17 (3H, d, $J = 7.0$ Hz), 1.06−1.05 (21H, m), 0.98 (9H, t, $J = 7.8$ Hz), 0.93 (9H, t, $J = 7.8$ Hz), 0.64 (6H, q, $J = 7.8$ Hz), 0.58 (6H, q, $J = 7.8$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 79.2, 75.3, 75.2, 73.7, 72.1, 69.0, 66.8, 65.2, 60.7, 46.0, 33.5, 27.9, 27.1, 18.9, 18.0, 16.6, 12.0, 7.0, 6.8, 6.8, 4.9; HRMS (CI, CH_4) *m*/*z* calcd for $C_{36}H_{74}O_7Si_3$ [M^+]: 702.4742, found: 702.4705 (Δ 5.3 ppm).

(3*R*,3a*R*,5*R*,6*R*,8*S*,9*S*,9a*R*)-6-Methyl-9-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-6,8-bis[(triethylsilyl)oxy]hexahydro-2*H*-3,5-ethanofuro[3,2-*b*]oxocine-3,9(3a*H*)-diol (39). Camphor sulfonic acid (CSA) (2.5 mg, 0.011 mmol) was added to a solution of the epoxide **38** (15.0 mg, 0.0213 mmol) in dry CH_2Cl_2 (2 mL) at room temperature under N_2. The reaction was heated to 40 °C and stirred at this temperature for 16 h. The reaction was allowed to cool to room temperature and then quenched by the addition of water (1 mL) and a saturated solution of sodium bicarbonate (1 mL). The mixture was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic extracts were washed with brine (5 mL), then dried ($MgSO_4$) and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (isohexane-ethyl acetate, 9:1 to 4:1) gave the tricyclic diol **39** (11.3 mg, 75%) as a colorless oil: $R_f = 0.69$ (isohexane-ethyl acetate, 4:1); $[\alpha]_D^{19}$ +18 ($c = 1.0$, $CHCl_3$); ν_{max} ($CHCl_3$) 3598, 3446, 2950, 2874, 910, 881 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.71 (1H, s), 4.38 (1H, d, $J = 4.7$ Hz), 4.36 (1H, d, $J = 5.3$ Hz), 3.96 (1H, d, $J = 9.3$ Hz), 3.96−3.92 (1H, m), 3.86 (1H, d, $J = 4.7$ Hz), 3.71 (1H, dd, $J = 10.1$, 4.5 Hz), 3.66 (1H, dd, $J = 11.2$, 6.7 Hz), 3.37 (1H, dd, $J = 9.3$, 1.1 Hz), 2.93 (1H, dd, $J = 14.7$, 5.3 Hz), 2.49−2.38 (1H, m), 1.93 (1H, dd, $J = 9.5$, 4.9 Hz), 1.86−1.78 (1H, m), 1.70−1.57 (2H, m), 1.48 (3H, s), 1.33 (1H, d, $J = 14.7$ Hz), 1.11−1.04 (24H, m), 0.98 (9H, t, $J = 7.8$ Hz), 0.93 (9H, t, $J = 7.8$ Hz), 0.72−0.55 (6H, m), 0.55 (6H, q, $J = 7.8$ Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 88.0, 84.4, 80.9, 79.5, 78.9, 78.7, 76.3, 76.2, 68.4, 43.6, 41.1, 32.1, 27.6, 19.8, 18.0, 12.7, 11.8, 7.2, 7.1, 7.0, 5.6; HRMS (CI, NH_4) *m*/*z* calcd for $C_{36}H_{74}O_7Si_3$ [$M]^+$: 702.4742, found: 702.4756 (Δ 2.0 ppm).

(3*R*,3a*R*,6*R*,8*S*,9*S*,9a*R*)-6-Methyl-9-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-6,8-bis[(triethylsilyl)oxy]hexahydro-3,5-(ethanylylidene)furo[3,2-*b*]oxocine-3,9(2*H*)-diol (41). Ruthenium(III) chloride hydrate (3.2 mg, 0.014 mmol) was added to a solution of the diol **39** (11 mg, 0.016 mmol) and sodium *m*-periodate (14 mg, 0.064 mmol) in CCl_4 (0.5 mL), acetonitrile (0.5 mL), and water (0.75 mL) at room temperature. The mixture was stirred at room temperature for 5 h and then diluted with CH_2Cl_2 (10 mL). The aqueous and organic layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were combined and washed with brine (5 mL), then dried ($MgSO_4$) and concentrated in vacuo. Purification by column chromatography on silica gel (petroleum ether-ethyl acetate, 9:1 to 4:1) gave recovered diol **39** (9 mg) and the alkene **41** (2 mg) as a colorless oil: $R_f = 0.43$ (petroleum ether-ethyl acetate, 4:1): $[\alpha]_D^{23}$ +39 ($c = 0.23$, $CHCl_3$); ν_{max} ($CHCl_3$) 3446, 2952, 2874, 1678, 1601, 883 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.20 (1H, dd, $J = 7.8$, 3.9 Hz), 4.68 (1H, br), 4.56 (1H, d, $J = 3.6$ Hz), 4.48 (1H, d, $J = 8.1$ Hz), 4.15 (1H, d, $J = 3.6$ Hz), 3.86 (1H, dd, $J = 11.6$, 10.4 Hz), 3.70 (1H, d, $J = 9.3$ Hz), 3.71−3.67 (1H, m), 3.41 (1H, dd, $J = 9.3$, 2.0 Hz), 2.83 (1H, dd, $J = 13.7$, 8.1 Hz), 2.56−2.47 (1H, m), 2.37 (1H, dd, 12.9, 7.8 Hz), 2.34−2.27 (1H, m), 1.64 (1H, d, $J = 13.7$ Hz), 1.47 (3H, s), 1.12−1.04 (21H, m), 0.98 (12H, t, $J = 7.9$ Hz), 0.95 (9H, t, $J = 8.0$ Hz), 0.76−0.62 (6H, m) 0.60 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 96.6, 88.9, 86.8, 83.5, 80.1, 79.5, 76.7, 75.3, 68.4, 50.7, 41.2, 32.4, 25.2, 18.0, 13.0, 11.8, 7.2, 7.1, 7.0, 5.3. HRMS (ESI) *m*/*z* calcd for $C_{36}H_{72}O_7Si_3$ [$M]^+$: 700.4586, found: 700.4528 (Δ 8.2 ppm).

(3*S*,3a*R*,5*R*,6*R*,8*S*,9*S*,9a*R*)-3,9-Dihydroxy-6-methyl-9-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-6,8-bis[(triethylsilyl)oxy]octahydro-2*H*-3,5-ethanofuro[3,2-*b*]oxocin-2-one (37) and (1*R*,2*S*,4*S*,5*S*,7*R*,8*R*)-7-Methyl-4-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-5,7-bis[(triethylsilyl)oxy]-3,12-dioxatricyclo-[6.3.1.0^{2,4}]dodecan-11-one (43). Tetra-*n*-butylammonium bromide (1.5 mg, 5.0 mol %) was dissolved in a saturated solution of sodium bicarbonate (180 μL), and the mixture was then added to a solution of the alcohol **38** (64 mg, 0.091 mmol) and TEMPO (0.7 mg, 5 mol %) in CH_2Cl_2 (2 mL) at room temperature. The mixture was cooled to 0 °C, and a solution of sodium hypochlorite (271 mg, 0.182 mmol) dissolved in a saturated solution of sodium bicarbonate (96 μL) and brine (198 μL) was added over 10 min. The reaction was stirred at 0 °C for 15 min and then quenched by the addition of water (10 mL) and CH_2Cl_2 (10 mL). The aqueous and organic phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to afford the crude aldehyde (69 mg) as a colorless oil.

The aldehyde was dissolved in a mixture of *t*-butanol (455 μL) and 2-methyl-2-butene (77 μL, 0.73 mmol) at room temperature. A solution of sodium chlorite (80%, 62 mg, 0.55 mmol) and sodium dihydrogenorthophosphate dihydrate (92 mg, 0.59 mmol) in water (910 μL) was then added dropwise over 5 min at room temperature. The mixture was stirred at room temperature for 15 min and then diluted with CH_2Cl_2 (10 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo to give the crude carboxylic acid **42** (69 mg) as a yellow oil.

The acid **42** (69 mg) was dissolved in dry CH_2Cl_2 (2 mL) and CSA (21 mg, 0.090 mmol) was added at room temperature under Ar. The reaction was stirred at room temperature for 45 min and then quenched by the addition of water (2 mL) and a saturated solution of sodium bicarbonate (2 mL). The phases were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic extracts were then combined, dried ($MgSO_4$), and concentrated in vacuo to give an oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 98:2 to 4:1) gave the

lactone **37** (24.4 mg, 37%) and the ketone **43** (27 mg, 44%) as colorless oils.

37: $R_f = 0.75$ (petroleum ether-ethyl acetate, 3:1); $[\alpha]_D^{22}$ −17 ($c = 1.0$, $CHCl_3$); ν_{max} ($CHCl_3$) 3422, 2952, 2874, 1777 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.94 (1H, s), 4.73 (2H, s), 4.45 (1H, d, $J = 5.0$ Hz), 4.03 (1H, dd, $J = 11.9$, 11.5 Hz), 3.83−3.76 (2H, m), 2.57−2.51 (1H, m, C*H*CH_3), 2.46 (1H, s), 2.44 (1H, dd, $J = 15.2$, 5.0), 2.10−2.04 (1H, m), 1.98−1.89 (1H, m), 1.73 (1H, ddd, $J = 14.3$, 11.9, 2.3 Hz), 1.50 (3H, s), 1.40 (1H, d, $J = 15.2$ Hz), 1.16−1.10 (1H, m), 1.07−1.04 (21H, m), 1.03 (3H, d, $J = 7.4$ Hz), 0.98 (9H, t, $J = 7.9$ Hz), 0.90 (9H, t, $J = 7.9$ Hz), 0.80−0.60 (6H, m), 0.54 (6H, q, $J = 7.9$ Hz); ^1H NMR (400 MHz, C_6D_6) key signals δ 5.16 (1H, d, $J = 5.3$ Hz, OCHC*H*OC═O/OC*H*CHOC═O), 5.13 (1H, d, $J = 5.3$ Hz, OCHC*H*OC═O/OC*H*CHOC═O); ^{13}C NMR (125 MHz, $CDCl_3$) δ 178.3, 85.2, 81.5, 79.5, 78.4, 76.2, 76.1, 75.9, 68.0, 44.0, 40.7, 27.6, 27.4, 21.9, 18.0, 12.2, 11.7, 7.2, 7.1, 6.9, 5.6; HRMS (CI, CH_4) *m*/*z* calcd for $C_{36}H_{72}O_8Si_3$ $[M]^+$: 716.4535, found: 716.4463.

43: $R_f = 0.50$ (petroleum ether-ethyl acetate, 19:1); $[\alpha]_D^{20}$ +2.2 ($c = 1.0$, $CHCl_3$); ν_{max} ($CHCl_3$) 2954, 2875, 1731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.38 (1H, s), 4.18 (1H, d, $J = 8.8$ Hz), 3.68 (1H, dd, $J = 9.7$, 4.6 Hz), 3.66 (1H, dd, $J = 10.6$, 3.6 Hz), 3.32 (1H, dd, $J = 9.7$, 6.9 Hz), 3.09 (1H, s), 2.62−2.53 (3H, m), 2.41−2.28 (2H, m), 1.89−1.76 (1H, m), 1.65 (1H, d, $J = 14.7$ Hz), 1.49 (3H, s), 1.19 (3H, d, $J = 7.0$ Hz), 1.08−1.00 (21H, m), 0.98 (9H, t, $J = 7.9$ Hz), 0.95 (9H, t, $J = 7.9$ Hz), 0.64 (6H, q, $J = 7.9$ Hz,), 0.59 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (125 Hz, $CDCl_3$) δ 209.4, 82.1, 78.9, 74.9, 72.2, 69.5, 64.4, 63.9, 46.1, 35.7, 33.9, 26.8, 19.7, 18.1, 17.0, 12.0, 7.1, 7.0, 6.9, 5.1; HRMS (CI, NH_3) *m*/*z* calcd for $C_{35}H_{70}O_6Si_3$ $[M]^+$: 670.4480, found: 670.4512 (Δ 4.7 ppm).

(3*S*,3a*R*,5*R*,6*R*,8*S*,9*S*,9a*S*)-3,9-Dihydroxy-6-methyl-9-{(1*R*)-1-methyl-2-[(triisopropylsilyl)oxy]ethyl}-6,8-bis[(triethylsilyl)oxy]-octahydro-2*H*-3,5-ethanofuro[3,2-*b*]oxocin-2-one (47). Potassium trimethylsilanolate (21 mg, 0.16 mmol) was added in one portion to a solution of the triol ester **35** (12 mg, 0.016 mmol) in dry ether (2 mL) at room temperature under Ar. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by the addition of 0.5 M HCl (10 mL) and extracted with ethyl acetate (3 × 10 mL). The ethyl acetate extracts were combined and washed with brine (5 mL), then dried ($MgSO_4$) and concentrated in vacuo to a clear oil. Purification by column chromatography on silica gel (hexane-ethyl acetate, 9:1) gave the lactone **47** (7 mg, 61%) as a colorless oil: $R_f = 0.78$ (petroleum ether-ethyl acetate, 3:1); $[\alpha]_D^{23}$ +7.1 ($c = 0.17$, $CHCl_3$); ν_{max} ($CHCl_3$) 3378, 2960, 2873, 1785, 1602 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.69 (1H, s), 4.70 (1H, d, $J = 10.3$ Hz), 4.61 (1H, d, $J = 10.3$ Hz), 4.31 (1H, dd, 11.6, 9.8 Hz), 4.09 (1H, d, $J = 8.1$ Hz), 3.82 (1H, dd, $J = 10.8$, 7.7 Hz), 3.59 (1H, dd, $J = 9.8$, 4.6 Hz), 2.80 (1H, dqd, $J = 11.6$, 7.1, 4.6 Hz), 2.63 (1H, s), 2.53−2.48 (1H, m), 2.35 (1H, dd, $J = 15.8$, 8.1 Hz), 1.97−1.71 (3H, m), 1.65 (1H, d, $J = 15.8$ Hz), 1.51 (3H, s), 1.07−1.05 (21H, m), 0.99 (9H, t, $J = 7.9$ Hz), 0.94 (3H, d, $J = 7.1$ Hz), 0.92 (t, 9H, $J = 7.9$ Hz,), 0.77−0.63 (6H, m), 0.56 (6H, q, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 79.2, 78.9, 78.5, 76.1, 75.5, 75.4, 71.5, 68.9, 48.2, 36.8, 29.8, 28.6, 20.7, 17.9, 17.9, 12.9, 11.7, 7.1, 6.9, 5.3; HRMS (ESI) *m*/*z* calcd for $C_{36}H_{72}O_8Si_3$ $[M]^+$: 716.4535, found: 716.4604 (Δ 9.6 ppm).

Acknowledgment. The University of Nottingham, Syngenta, and Merck Sharp and Dohme are gratefully acknowledged for studentship funding (for C.A.B. and A.G.D.). This work was supported by EPSRC (U.K.) (Grant GR/L62856/01).

Supporting Information Available: ^1H and ^{13}C NMR spectra for **7**, **8**, **11**−**13**, **15**−**19**, **21**, **23**−**30**, **33**−**35**, **37**−**39**, **41**, **43**, and **47**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO702111U