Hydroxy-Directed Diastereoselective Installation of a Methyl Group on Indalone Models and Spiroketal Potential Precursors for the Bafilomycin A_1 C15−C25 Subunit

Jean-Christophe Poupon, Roman Lopez, Joëlle Prunet,* and Jean-Pierre Férézou*,†

Laboratoire de Synthèse Organique associé au CNRS, UMR 7652, Ecole Polytechnique, DCSO, 91128 Palaiseau, France

joelle.prunet@polytechnique.fr

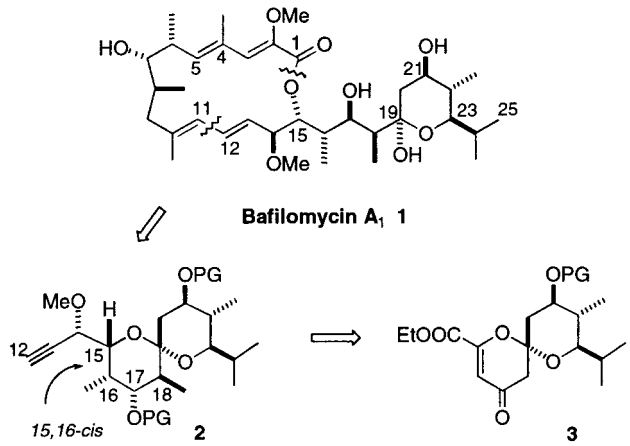
Received October 24, 2001

Current efforts devoted to the synthesis of Bafilomycin A_1 led us to investigate a synthetic route through a spiroketal intermediate for the construction of the C15−C25 subunit. Preliminary studies for the diastereoselective installation of the methyl-16 *cis* with respect to the vicinal OH-15 group through radical opening of either siloxafuran intermediate **7** or cyclopropyl compounds **9** and **13** have been carried out using model compounds derived from commercial Indalone **6**. In each case the expected "*cis*" diastereoisomer was obtained in good to excellent yield. Application of these results to Bafilomycin A_1 synthon led to the opposite "*trans*" stereoselectivity when α-carboxy- or α-keto-substituted spiroketals **4** or **19** were used. However, the expected potential intermediate has been obtained from the α-hydroxymethyl cyclopropanated synthon **21**. A Barton−Motherwell xanthate radical deoxygenation−cylopropane opening methodology, followed by a hydroboration−oxidation of the exovinylic intermediate, delivered the expected product **22*cis*** in high yield and excellent stereoselectivity.

Introduction

Bafilomycin A_1 **1** is a 16-membered macrolide first isolated from the broth of *Streptomyces griseus* in 1984 by Werner et al.[1] As a result of its potent biological activities and particularly its unique specific inhibitory effect on vacuolar-type proton translocating ATP-ases (V-ATPases),[2] Bafilomycin A_1 continues to interest organic chemists, and three total syntheses of **1** as well as significant partial contributions have been reported so far.[3] Moreover, extensive chemical studies have been devoted to the synthesis of derivatives possessing improved specificity in inhibiting the V-ATPases overexpressed in the bone-resorbing osteoclasts, a major metabolic disorder associated with osteoporosis.[4]

Scheme 1



Our current efforts to develop an original route for the total synthesis of Bafilomycin A_1[5] led us to envision construction of this molecule as shown in Scheme 1. The macrolide ring can be opened and then disconnected between C-11 and C-12 via a Stille- or Suzuki-type coupling reaction. The resulting C12−C25 fragment would be synthesized from fully substituted spiroketal **2** by opening of the spiroketal moiety and straightforward conversion of the alkyne terminus to the required activated vinyl function.

The choice of a spiroketal precursor was dictated by the possibility of installing various substituents with

† Far-Manguinhos, Fundação Oswaldo Cruz, Laboratório de Síntese Orgânica, Rua Sizenando Nabuco 100, Manguinhos, CEP 21041-250 Rio de Janeiro/RJ, Brazil. E-mail: ferezou@gbl.com.br.

(1) Werner, G.; Hagenmaier, H.; Albert, K.; Kohlshorn, H.; Drautz, H. *Tetrahedron Lett.* **1983**, *24*, 5193. Werner, G.; Hagenmaier, H.; Drautz, H.; Baumgartner, A.; Zähner, H. *J. Antibiot.* **1984**, *37*, 110. For structure elucidation: Corey, E. J.; Ponder, J. W. *Tetrahedron Lett.* **1984**, *25*, 4325. Baker, G. H.; Brown, P. J.; Dorgan, R. J. J.; Everett J. R.; Ley, S. V.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron Lett.* **1987**, *28*, 5565.

(2) Bowman, E. M.; Siebers, A.; Altendorf, K. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7972.

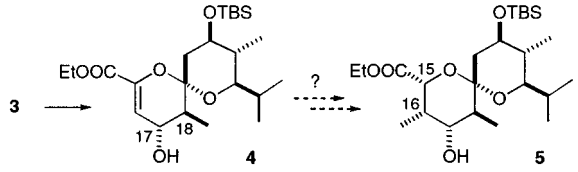
(3) Total syntheses: (a) Evans, D. A.; Calter, M. A. *Tetrahedron Lett.* **1993**, *34*, 6871. (b) Toshima, K.; Jyojima, T.; Yamaguchi, H.; Murase, H.; Yoshida, T.; Matsumura, S.; Nakata, M. *Tetrahedron Lett.* **1996**, *37*, 1069. Toshima, K.; Yamaguchi, H.; Jyojima, T.; Noguchi, Y.; Nakata, M.; Matsumura, S. *Tetrahedron Lett.* **1996**, *37*, 1073. Toshima, K.; Jyojima, T.; Noguchi, Y.; Yoshida, T.; Murase, M.; Nakata, M.; Matsumura, S. *J. Org. Chem.* **1997**, *62*, 3271. (c) Scheidt, K. A.; Tasaka, A.; Bannister, T. D.; Wendt, M. D.; Roush, W. R. *Angew. Chem., Int. Ed.*. **1999**, *38*, 1652. Partial contributions: (d) Roush, W. R.; Bannister, T. D. *Tetrahedron Lett.* **1992**, *33*, 3587. Roush, W. R.; Bannister, T. D.; Wendt, M. D. *Tetrahedron Lett.* **1993**, *34*, 8387. (e) Paterson, I.; Bower, S., McLeod, M. D. *Tetrahedron Lett.* **1995**, *36*, 175. (f) Hanessian, S.; Wang, W.; Gai, Y., Olivier, E. *J. Am. Chem. Soc.* **1997**, *119*, 10034. (g) Breit, B.; Zahn, S. K. *Tetrahedron Lett.* **1998**, *39*, 1901. (h) Marshall, J. A.; Adams, N. D. *Org. Lett.* **2000**, *2*, 2897. Total syntheses of the related Concanamycin F: (i) Toshima, K.; Jyojima, T.: Miyamoto, N.; Katohno, M.; Nakata, M.; Matsumara, S. *J. Org. Chem.* **2001**, *66*, 1708. (j) Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int. Ed.*. **2000**, *39*, 1308.

(4) Review: Gagliardi, S.; Rees, M.; Farina, C. *Curr. Med. Chem.* **1999**, *6*, 1197.

(5) Previous publication for the synthesis of the C1−C5 subunit: Demont, E.; Lopez, R.; Férézou, J.-P. *Synlett* **1998**, 1223.

10.1021/jo016231l CCC: $22.00
Published on Web 03/13/2002

Scheme 2



excellent diastereocontrol on such a rigid template, provided one or a few pivotal stereogenic centers were already in place. Although not widely used, such a strategy has already been successfully developed for the synthesis of nonspiroketal targets.[6] Such an approach should be expected to allow cost-effective construction of complex carbon skeleton units exhibiting numerous vicinal stereogenic centers.

Therefore the C-15, C-16, C-17 and C-18 stereogenic centers of **2** were proposed to be accessible from the rather simple spiroketalic enone **3**, taking advantage of the chirality present in the other six-membered ring of the spiroketal substructure to generate the missing stereogenic centers. Interestingly, spiroketal **3** has been already synthesized as an epimeric precursor at C-21 for the synthesis of the antihelminthic spirocyclic macrolide Avermectins of series 2.[7]

According to this strategy, the unsaturated homochiral spiroketal **4** was synthesized by treating ketone **3** with NaHMDS/MeI and reducing the carbonyl group with an appropriate reducing agent (Scheme 2).[8]

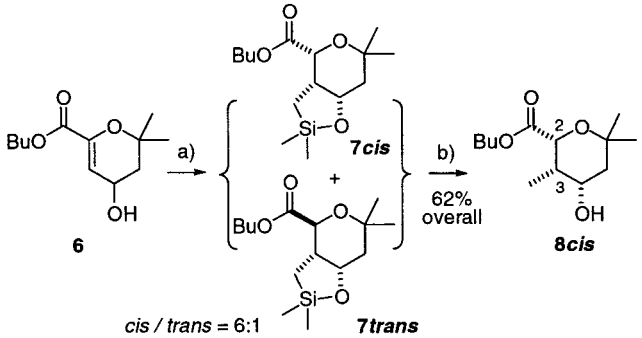
However, the subsequent installation of the methyl group at C-16 in a *cis* configuration with respect to both the vicinal OH-17 and the C-15 side chain in **5** revealed a more complex challenge than expected, and preliminary model studies were carried out to test several possible strategies to reach this goal. This paper deals with the results of our efforts in this direction, initially developed on indalone-derived models and subsequently applied to potential Bafilomycin A_1 spiroketal synthons.[9]

Results and Discussion

Model Studies with Indalone. Alcohol **6**, easily obtained by $NaBH_4$ reduction (80%) of commercial butopyronoxyl (Indalone), was elected as a simple model substrate.

Stork's TPS Methodology. The first approach we considered used Stork's methodology involving *cis*-directed radical formation of bicyclic siloxafurans intermediates followed by tributyltin hydride triggered fragmentation (temporary silicon connection or TPS).[10] Reaction of **6** with bromomethyldimethylchlorosilane in the presence of triethylamine led to the expected silyl ether (Scheme 3). This labile intermediate was not purified but directly subjected to tributyltin hydride/AIBN treatment in toluene at reflux. Bicyclic product **7** was obtained as a non-separable 6:1 mixture of *cis*/*trans* epimers.[11] Fluoride treatment of the mixture followed by column chromatography provided pure **8*cis***.[12] The overall yield of the process is good (62%), and all of the stereocenters exhibit the relative configuration required for Bafilomycin A_1 synthesis.

Scheme 3[a]



[a] Reagents: (a) (i) $BrCH_2Me_2SiCl$, Et_3N, DMAP; (ii) Bu_3SnH, AIBN, Tol, reflux; (b) TBAF, DMF, 65 °C, flash chromatography.

We next investigated other routes involving as the key step radical regio- and stereocontrolled opening of intermediate cyclopropanes prepared from **6**. The main advantages of these cyclopropane approaches is the general ease of preparation of the required cyclopropyl intermediates, generally in good yields, together with the excellent stereocontrol expected from OH-directed cyclopropanation reaction of allylic alcohols such as **6**.[13] Preliminary studies using described strategies involving electrophilic opening of cyclopropanes, particularly the NIS/MeOH Danishefsky's methodology[14] as well Nagarajan mercurate conditions,[15] resulted in disappointment, leading either to starting material or complex mixtures with various amounts of ring expansion products. We therefore decided to turn our attention to radical processes. One main problem to be anticipated for the cyclopropane ring-opening step is the competitive ring-expansion process leading to the seven-membered ring-expansion product instead of the desired cyclopropane fragmentation affording the methyltetrahydropyran.

Two different methodologies have been tested on indalone-derived models:

Reductive Radical Opening of α-Acyl-α,β-cyclopropanated Tetrahydropyrans such as 9 in the

(6) Representative examples: Hoye, T. R.; Peck, D. R.; Swanson, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 2738. Bernet, B.; Bishop, P. M.; Caron, M.; Kawamata, T.; Roy, B. L.; Ruest, L.; Sauvé, G.; Soucy, P.; Deslongchamps, P. *Can. J. Chem.* **1985**, *63*, 2818 and preceding communications in the issue. Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312. Schreiber, S. L.; Wang, Z. *J. Am. Chem. Soc.* **1985**, *107*, 5303. Totah, N. I.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 6255. Zhao, Y.; Pratt, N. E.; Heeg, M. J.; Albizati, K. F. *J. Org. Chem.* **1993**, *58*, 1300. Martin, S. F.; Lee, W.-C. Pacofsky, G. J.; Gist, R. P.; Mulhern, T. A. *J. Am. Chem. Soc.* **1994**, *116*, 4674. Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048. Ireland, R. E.; Longbin, L.; Roper, T. D. *Tetrahedron* **1997**, *53*, 13221. Ireland, R. E.; Longbin, L.; Roper, T. D.; Gleason, J. L. *Tetrahedron* **1997**, *53*, 13257.

(7) Barrett, A. G. M.; Raynham, T. M. *Tetrahedron Lett.* **1987**, *28*, 5615.

(8) To be published elsewhere.

(9) All products described throughout this paper are racemic and depicted configurations are relative.

(10) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500. For a review on the temporary silicon connection, see: Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813.

(11) Throughout this paper, the terms or suffixes *cis* and *trans* refer to epimers at the C-2 center for model compounds or at the C-15 center for Bafilomycin precursors with respect to the vicinal methyl group at C-3 or C-16, respectively. For clarity, Bafilomycin carbon numbering has been used for all spiroketal precursors.

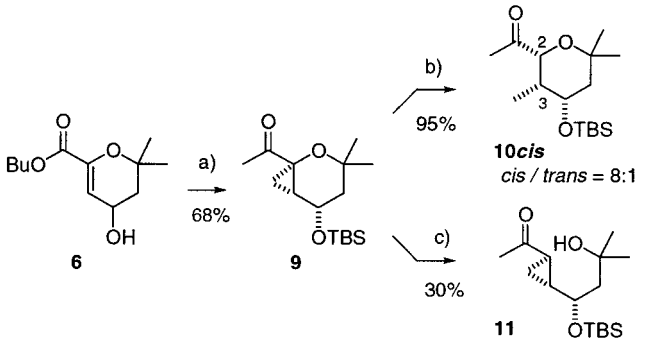
(12) The relative stereochemistry of **8*cis*** and **8*trans*** has been deduced from ^1H NMR spectroscopy; $J_{2,3} = 2.3$ Hz for the 2,3-*cis* and 10.4 Hz for the 2,3-*trans* epimer, respectively.

(13) For a recent review on the chemistry of cyclopropanated tetrahydropyrans, see: Cousins, G. S.; Hoberg, J. O. *Chem. Soc. Rev.* **2000**, *29*, 165.

(14) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000.

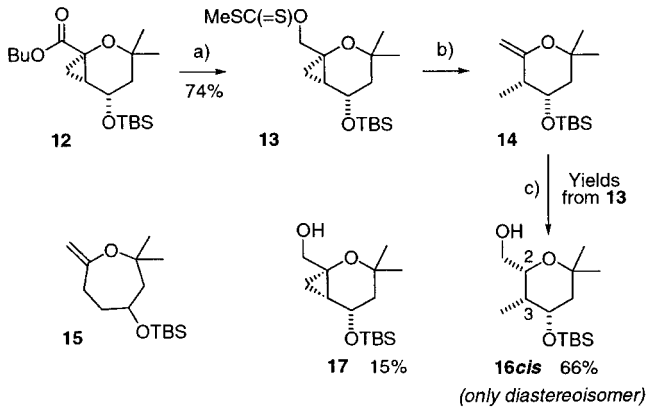
(15) Ramana, C. V.; Murali, R.; Nagarajan, M. *J. Org. Chem.* **1997**, *62*, 7694. Ramana, C. V.; Nagarajan, M. *Synlett*, **1997**, 763. Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615.

Scheme 4[a]



[a] Reagents: (a) (i) Et_2Zn, CH_2I_2, O_2, 89%; (ii) TBSCl, Im, 95%; (iii) *i*-PrMgCl, MeO(Me)NH·HCl; (iv) MeLi, 81% (2 steps); (b) Bu_3SnH, AlBN, Tol, reflux; (c) SmI_2, HMPA, THF.

Scheme 5[a]



[a] Reagents: (a) (i) DIBAL-H; (ii) NaH, CS_2, MeI; (b) (i) Bu_3SnH, AlBN, Tol, reflux; (c) BH_3·THF; H_2O_2, NaOH.

Presence of Tributyltin Hydride. Radical opening of α,*β*-cyclopropanated cyclohexanones[16] or α-keto-α,*β*-cyclopropanated cyclohexanes (see below for samarium iodide promoted reactions) has already been described in the literature but, to our knowledge, has not yet been studied in the case of tetrahydropyran equivalents. The Bu_3SnH/AIBN conditions used by Enholm et al. for α-ketocyclopropanes were selected.[17] To test these conditions, preliminary transformation of the ester function of **6** into a corresponding ketone function had to be accomplished. Alcohol **6** was readily transformed into α-cyclopropyl ketone **9** in four steps (Scheme 4): Simmons−Smith cyclopropanation under Miyano conditions led, in 89% yield, to a single adduct bearing the cyclopropane *cis* to the hydroxyl group.[18] Further protection of the secondary alcohol as its TBS ether followed by conversion of the butyl ester function into the corresponding methyl ketone via the corresponding Weinreb amide, realized according to Williams et al.,[19] allowed preparation of **9** in 68% yield from **6**.

The subsequent cyclopropane radical opening reaction of **9** required extensive investigation. Unsatisfactory results were obtained under classical tributyltin hydride/AIBN stoichiometric conditions. However, in the presence large excess of hydride (7 equiv) and of AIBN (2.5 equiv) in refluxing toluene with syringe-pump addition of the substrate to the reaction mixture, the expected methylated derivative **10*cis*** was obtained in 95% yield as a 8:1 mixture of *cis*/*trans* isomers that could be easily separated by column chromatography.[20]

Attempted Cyclopropane Opening of 9 with Samarium Iodide. As radical opening of α-cyclopropyl methyl ketones has been demonstrated to occur efficiently in the presence of samarium iodide,[21] these one-electron reducing conditions were subsequently tested. Unfortunately the only isolated product was the tertiary alcohol **11** (30% yield) resulting from opening of the tetrahydropyran ring instead of the cyclopropyl ring, a result in agreement with the known reductive cleavage of α-heterosubstituted carbonyl compounds mediated by SmI_2.[22]

Radical Opening of Xanthate 13 Derived from α-Hydroxymethyl α,*β*-Cyclopropanated Tetrahydropyrans such as 17 under Barton's Conditions.[23] Tributyltin hydride promoted reductive deoxygenation−cyclopropane opening of xanthate **13**, prepared in two steps from ester **12** in 74% yield, was then tested (Scheme 5). Treatment of **13** with Bu_3SnH/AIBN in toluene at reflux furnished the exocyclic vinyl derivative **14** occurring from cyclopropane fragmentation, with no detectable trace of the corresponding ring-expanded product **15**. The unstable exo olefinic adduct **14**, prone to facile endocyclic double bond migration, was submitted without purification to a hydroboration−oxidation reaction to give the alcohol **16*cis*** as a single isomer in a 66% yield from **13**.[24] A side-product was obtained in 15% yield: alcohol **17**, precursor of xanthate **13**.[25] It is important to point out that this result is significantly different from a literature precedent of Gurjar and co-workers during Bu_3SnH/AIBN-promoted opening of an α-bromomethyl α-cyclopropyl deoxysugar.[26] These authors obtained a 2:3 mixture of oxepane/methylpyranose products.

At this level, three different methods, Stork's TPS methodology, tributyltin hydride promoted opening of a α-keto-α-cyclopropyltetrahydropyrane precursor, or tributyltin hydride reductive deoxygenation−cyclopropane

(16) Batey, R. A.; Harling, J. D.; Motherwell, W. B. *Tetrahedron* **1992**, *48*, 8031. Batey, R. A.; Harling, J. D.; Motherwell, W. B. *Tetrahedron* **1996**, *52*, 11421 and references therein.

(17) Enholm, E. J.; Jia, Z. J. *J. Org. Chem.* **1997**, *62*, 5248 and 9159. See also references cited. For precedents in this area, see: Pereyre, M.; Quintard, J. P.; Rahm, A. *Tin in Organic Synthesis*; Butterworth: Boston, 1987.

(18) Miyano, S.; Matsumoto, Y.; Hashimoto, H. *J. Chem. Soc., Chem. Commun.* **1975**, 364.

(19) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461.

(20) The relative stereochemistry was determined by ^1H NMR spectroscopy; $J_{2,3} = 2.5$ Hz for the 2,3-*cis* and 10.5 Hz for the 2,3-*trans* epimer, respectively.

(21) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112. Batey, R. A.; Motherwell, W. B. *Tetrahedron Lett.* **1991**, *32*, 6211. See also ref 13. Molander, G. A.; Alonso-Alija, C. *Tetrahedron* **1997**, *53*, 8067 and references therein. Nivlet, A.; Le Guen, V.; Dechoux, L.; Le Gall, T.; Mioskowski, C. *Tetrahedron Lett.* **1998**, *39*, 2115. Reutrakul, V.; Saeeng, R.; Pohmakotr, M. Kongsaeree, P. *Tetrahedron Lett.* **1999**, *40*, 1019. Kusama, H.; Hara, R.; Kawahara, S.; Nishimori, T.; Kashima, H.; Nakamura, N.; Morihira, K.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 3811. Reviews on samarium iodide: Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley: New York, 1994; Vol. 46, p 211. Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321.

(22) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. For α-epoxyketones, see: Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 2596. For a recent example of cyclic ether opening induced by SmI_2, see: Yoshida, A.; Takayama, H. *Tetrahedron Lett.* **2001**, *42*, 3603.

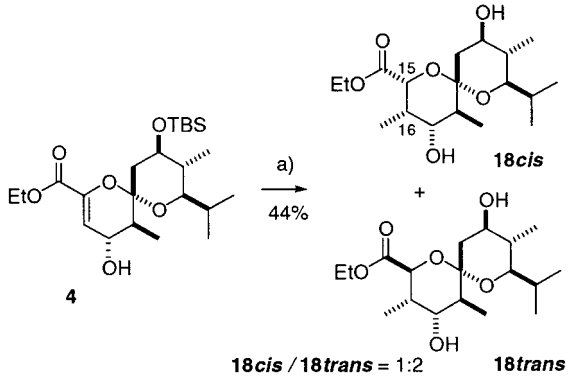
(23) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

(24) The stereochemistry of **16*cis*** was determined by ^1H NMR spectroscopy: $J_{2,3} = 2.0$ Hz for the bis TBS derivative.

(25) This type of side product is often obtained in the case of primary xanthates; see ref 23.

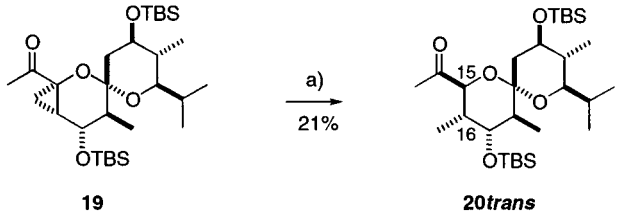
(26) Gurjar, M. K.; Chakrabarti, A.; Rao, B. V.; Kumar, P. *Tetrahedron Lett.* **1997**, *38*, 6885.

Scheme 6[a]



[a] Reagents: (a) (i) $BrCH_2Me_2SiCl$, Et_3N, DMAP; (ii) Bu_3SnH, AlBN, Tol, reflux; (iii) TBAF, DMF, 65 °C.

Scheme 7[a]



[a] Reagents: (a) Bu_3SnH, AlBN, toluene, reflux.

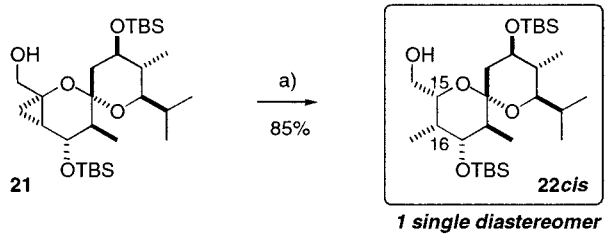
ring opening of an α-hydroxymethyltetrahydropyranyl xanthate have been developed to install a methyl group in an α-*cis* position of an hydroxyl group on Indalone-derived models. These conditions were subsequently applied to suitable precursors of Bafilomycin A_1.

Application to Spiroketal Precursor of Bafilomycin A_1. The three preceding methodologies have been subsequently applied to the required spirocyclic precursor **4** of the C15−C25 fragment of Bafilomycin A_1 in order to install both C-15 and C-16 stereogenic centers with the desired configuration. This precursor was synthesized according to our recently published acetonyl−tetrahydropyran methodology.[27]

In a first set of experiments, Stork's TPS methodology was applied to the unsaturated hydroxy ester **4** (Scheme 6). The expected methylated products **18** were obtained in 44% yield, but unfortunately with a 2:1 ratio in favor of the undesired **18*trans*** epimer.[28] The reason for this reversed selectivity remains unclear.[29] All efforts attempted to convert **18*cis*** into **18*trans*** under basic conditions (DBU/THF) led to decomposition of the spiroketal derivative.

We next turned to the cyclopropane-opening methodologies. As shown in Scheme 7, tributyltin hydride treatment of α-cyclopropyl ketone **19**, prepared from **4** according to a route similar to the one described for **9**,[8] delivered in low yield a single methylated ketone that was demonstrated to be **20*trans***[30] together with 35% of recovered starting material. Here again, the undesired 15,16-*trans* isomer is favored in the spiroketal case.

Scheme 8[a]



[a] Reagents: (a) (i) NaH, CS_2, MeI; (ii) Bu_3SnH, AlBN, toluene, reflux; (iii) BH_3·THF; H_2O_2, NaOH.

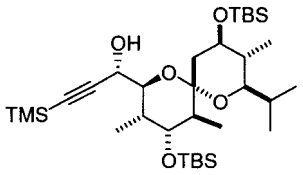
Radical opening of the α-hydroxymethylcyclopropane derivative **21** was finally addressed. This precursor was thought to be able to produce the expected 15,16-*cis* diastereomer. Reaction of the xanthate derived from alcohol **21**[8] with Bu_3SnH/AIBN followed by a hydroboration−oxidation reaction under the conditions developed during the preceding model experiments led to the spirocyclic alcohol **22** exhibiting the expected 15,16-*cis* relative configuration in an excellent 85% overall yield (Scheme 8).[31] No trace of the corresponding *trans*-isomer was detected, indicating as expected an exclusive hydroboration reaction from the less hindered upper face of the intermediate exocyclic olefin.

Conclusion

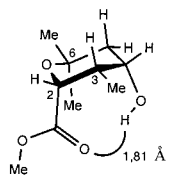
Various methods have been tested to install the C-16 methyl group as well as the C-15 vicinal center on a potential spirocyclic precursor of Bafilomycin A_1 with a high stereoselectivity. Extensive studies on models derived from Indalone have demonstrated that α-keto or xanthate activated α-hydroxymethyl-cylopropyltetrahydrofuran intermediates can deliver the expected methylated products with good stereoselectivity and without formation of the corresponding seven-membered expan-

(27) Henryon, V.; Liu, L. W.; Lopez, R.; Prunet, J.; Férézou, J.-P. *Synthesis* **2001**, 2401. The configuration of all stereocenters of compound **4** was proved by X-ray crystallography of a later intermediate in the synthesis; see ref 28.

(28) Structure of **18*trans*** was ascertained by X-ray crystallography of a later intermediate (to be published elsewhere):



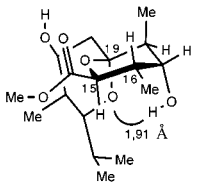
(29) Results of computational calculations (Chem3D Pro, CSC, MM2) indicate opposite thermodynamically favored diastereomers in the case of indalone derivatives versus spiroketal adducts. Intramolecular hydrogen bonding stabilization seems to be decisive in both cases (the depicted conformations are in agreement with ^1H NMR data), but it has not been proven that the ring-opening with TBAF is under thermodynamic control.



Most stable C-2 epimer
(2,3-*cis*)

ΔΔG *cis-trans* = 12 kJ/mol

Indalone® model **8*cis***



Most stable C-15 epimer
(15,16-*trans*)

ΔΔG *trans-cis* = 6 kJ/mol

Bafilomycin A_1 precursor **18*trans***

(30) Stereochemistry of **20*trans*** was determined by chemical correlation through transformation of the ethyl ester function of the bis(OTBS) ether derived from **18*trans*** into the corresponding methyl ketone (via the Weinreb amide).

(31) Stereochemistry of **22*cis*** was determined by chemical correlation with the product of DIBAL-H reduction of the bis(OTBS) ether derived from **18*cis***.

sion rings. The present study provides an as yet unexplored insight in the radical chemistry of this cheap commercial starting material.

In the case of the synthesis of Bafilomycin A_1, a Barton−Motherwell xanthate reductive deoxygenation−cyclopropyl opening process followed by a hydroboration−oxidation reaction appears to be the best way to generate the C-15 and C-16 centers with high yield and total stereocontrol. Application of these results to the synthesis of Bafilomycin A_1 is currently under investigation. The present study demonstrates that α-substituted-α,β-cyclopropanated tetrahydropyrans are good substrates for radical mediated methylation reactions, and the results presented here should find other synthetic applications in the synthesis of natural products from carbohydrate building blocks.

Experimental Section

For general methods, see ref 32.

Butyl (2*R,3*S**,4*S**)-2,2,6,6-Tetramethylhexahydro-1,5-dioxa-2-silaindene-4-carboxylate (7*cis*).** To a solution of 500 mg (2.2 mmol) of alcohol **6** in 8 mL of CH_2Cl_2 at 0 °C was added 2.2 mL (15.8 mmol, 7.2 equiv) of triethylamine, followed by 600 μL (4.3 mmol, 2.0 equiv) of bromomethyldimethylsilyl chloride and 13 mg (0.11 mmol, 0.05 equiv) of DMAP. The resulting solution was stirred at 0 °C for 45 min before it was quenched with 97 μL (2.4 mmol, 1.1 equiv) of methanol and 25 mL of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase was extracted with 10 mL of ether. The combined organic layers were washed with water and brine, then dried over Na_2SO_4, filtered and concentrated in vacuo to give the desired labile *O*-bromomethyldimethyldisiloxy intermediate. This product was kept in the dark and used as soon as possible for the next step without purification. IR (film) ν 2960, 1735, 1646, 1456, 1386, 1254, 1216, 1153, 1103, 1071 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (d, 1H, J = 3.2 Hz), 4.52 (ddd, 1H, J = 3.2, 6.5, 6.7 Hz), 4.19 (t, 2H, J = 6.8 Hz), 2.50 (s, 2H), 1.93 (dd, 1H, J = 6.3, 13.6 Hz), 1.76 (dd, 1H, J = 7.3, 13.6 Hz), 1.67 (quint, 2H, J = 7.1 Hz), 1.41 (s, 3H), 1.43−1.33 (m, 2H), 1.30 (s, 3H), 0.95 (t, 3H, J = 7.4 Hz), 0.32, 0.31 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 163.2, 143.9, 110.3, 76.6, 65.2, 61.9, 42.4, 30.9, 27.5, 26.2, 19.3, 16.1, 13.7, −2.3. MS (CI, NH_3) *m*/*z* 398, 396 ($M + NH_4^+$), 381, 379 ($M + H^+$).

To a solution of the previous unpurified bromomethylsilyl ether in 44 mL of toluene at reflux was added a solution of 18 mg (0.11 mmol, 0.05 equiv) of AIBN and 880 μL (1.5 mmol, 3.3 equiv) of Bu_3SnH in 8 mL of toluene (degassed by bubbling argon during 10 min). The reaction mixture was stirred at reflux for 2.5 h, cooled to 20 °C, and diluted with CH_2Cl_2 and the solvents were evaporated in vacuo to furnish **7** as a 6:1 mixture of *cis*/*trans* isomers. ^1H NMR (400 MHz, $CDCl_3$, ***7cis*** signals reported) δ 4.46 (d, 1H, J = 3.3 Hz), 4.40 (td, 1H, J = 6.0, 11.6 Hz), 4.18 (t, 3H, J = 6.7 Hz), 2.51 (dddd, 1H, J = 3.3, 6.5, 6.7, 13.2 Hz), 1.75 (dd, 1H, J = 5.6, 13.3 Hz), 1.68−0.84 (m, 11H), 1.20 (s, 3 H), 0.48 (dd, 1H, J = 6.8, 14.2 Hz), 0.27, 0.18 (2s, 6H). MS (CI, NH_3) *m*/*z* 318 ($M + NH_4^+$), 301 ($M + H^+$).

Butyl (2*R,3*S**,4*S**)-4-Hydroxy-3,6,6-trimethyltetrahydropyran-2-carboxylate (8*cis*).** The previous unpurified product **7** (6:1 *cis*/*trans* mixture) was dissolved in 30 mL of DMF, and the resulting solution was treated with 3.4 g (11 mmol, 5.0 equiv) of TBAF·$3H_2O$ and heated at 65 °C for 2 h. The reaction mixture was cooled to 20 °C and partitioned between 150 mL of ether, 75 mL of saturated aqueous NH_4Cl, and 60 mL of water. The layers were separated and the aqueous phase was extracted with 2 × 50 mL of EtOAc. The combined organic layers were washed with water and brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 10:90 to 60:40) gave in order of elution 332 mg (62% for three steps) of ***8cis*** as a colorless oil and 33 mg (10%) of ***8trans*** as a colorless oil.

***8cis*:** IR (film) ν 3455, 2970, 1748, 1463, 1373, 1194, 1124, 1061, 1029 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.25 (d, 1H, J = 2.3 Hz), 4.18−4.09 (m, 3H), 2.36−2.28 (m, 1H), 1.62 (quint, 2H, J = 7.2 Hz), 1.57, 1.51 (2d, 2H, J = 12.7 Hz), 1.44−1.31 (m, 2H), 1.35, 1.22 (2s, 6H), 0.92 (t, 3H, J = 7.6 Hz), 0.85 (d, 3H, J = 6.9 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.8, 73.8, 72.9, 67.9, 64.7, 39.8, 37.5, 31.6, 31.0, 23.0, 19.3, 13.6, 13.5. MS (CI, NH_3) *m*/*z* 262 ($M + NH_4^+$), 245 ($M + H^+$). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 64.01; H, 10.04.

***8trans*:** IR (film) ν 3508, 2963, 2876, 1732, 1457, 1382, 1227, 1174, 1087, 1065 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.23 (d, 1H, J = 10.4 Hz), 4.15 (t, 2H, J = 6.7 Hz), 4.03−3.98 (m, 1H), 1.86 (dqd, 1H, J = 2.8, 7.1, 10.3 Hz), 1.77, 1.72 (2dd, 2H, J = 3.0, 14.5 Hz), 1.64 (quint, 2H, J = 7.1 Hz), 1.47−1.31 (m, 2H), 1.41, 1.25 (2s, 6H), 0.94 (t, 3H, J = 7.6 Hz), 0.92 (d, 3H, J = 7.1 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.0, 72.4, 72.1, 69.0, 64.7, 42.8, 37.1, 32.1, 30.7, 25.3, 19.2, 13.7, 12.8. MS (CI, NH_3) *m*/*z* 262 ($M + NH_4^+$), 245 ($M + H^+$).

Butyl (1*S,5*S**,6*S**)-5-(*tert*-Butyldimethylsiloxy)-3,3-dimethyl-2-oxabicyclo[4.1.0]heptane-1-carboxylate (12).** To a solution of 4.56 g (20 mmol) of alcohol **6** in 100 mL of toluene at 20 °C was added 54.6 mL (60 mmol, 3 equiv) of 1.1 M Et_2Zn in toluene, causing gas evolution. After 30 min of stirring at this temperature, 4.8 mL (60 mmol, 3 equiv) of CH_2I_2 was added and dry air was passed through the solution, causing an exothermic reaction. The yellow solution then became a milky white suspension, and the reaction mixture was stirred at 20 °C for 2 h and treated with 100 mL of 1 M aqueous HCl. The layers were separated and the aqueous phase was extracted with 3 × 20 mL of ethyl acetate. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, water, and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 60:40 to 80:20) gave 4.29 g (89%) of the desired cyclopropanated alcohol as a clear yellow oil. IR (film) ν 3446, 2964, 1718, 1466, 1397, 1297, 1176, 1051 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.46 (td, 1H, J = 6.7, 11.0 Hz), 4.21 (td, 1H, J = 6.6, 10.8 Hz), 4.05 (td, 1H, J = 6.5, 10.8 Hz), 2.09 (ddd, 1H, J = 7.4, 8.0, 10.2 Hz), 1.87 (br s, 1H), 1.81 (dd, 1H, J = 7.2, 13.4 Hz), 1.66−1.59 (m, 2H), 1.50 (dd, 1H, J = 5.2, 10.3 Hz), 1.38 (sext, 2H, J = 7.4 Hz), 1.24, 1.15 (2s, 6H), 1.14 (dd, 1H, J = 10.8, 12.1 Hz), 1.06 (dd, 1H, J = 5.1, 8.1 Hz), 0.93 (t, 3H, J = 7.4 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.3, 75.5, 65.2, 62.2, 58.9, 40.9, 30.8, 29.9, 26.3, 22.9, 19.4, 19.2, 13.7. MS (CI, NH_3) *m*/*z* 260 ($M + NH_4^+$), 243 ($M + H^+$). Anal. Calcd for $C_{13}H_{22}O_4$: C, 64.44; H, 9.15. Found: C, 64.37; H, 9.37.

To a solution of 3.89 g (16 mmol) of the preceding alcohol in 32 mL of DMF at 20 °C was added 3.29 g (48.2 mmol, 3 equiv) of imidazole. The resulting solution was cooled to 0 °C and treated with 3.64 g (24.1 mmol, 1.5 equiv) of TBSCl. After stirring for 5 h at 20 °C, the reaction mixture was treated with 5 mL of methanol and 30 min later with 200 mL of ether. The organic phase was washed 3 times with water, with brine, then dried over $MgSO_4$, filtered and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 20:80) gave 5.39 g (95%) of silyl ether **12** as a colorless oil. IR (film) ν 2957, 1744, 1721, 1471, 1366, 1296, 1254, 1204, 1181, 1085 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (td, 1H, J = 6.8, 10.7 Hz), 4.22 (td, 1H, J = 6.7, 10.8 Hz), 4.05 (td, 1H, J = 6.6, 10.8 Hz), 1.94 (ddd, 1H, J = 6.8, 8.1, 10.3 Hz), 1.65 (dd, 1H, J = 7.3, 13.8 Hz), 1.64 (m, 2H), 1.47 (dd, 1H, J = 5.1, 10.4 Hz), 1.40 (dsext, 2H, J = 2.1, 7.4 Hz), 1.22 (s, 3H), 1.21 (dd, 1H, J = 11.0, 13.0 Hz), 1.15 (s, 3H), 1.10 (dd, 1H, J = 5.1, 8.2 Hz), 0.95 (t, 3H, J = 7.4 Hz), 0.90 (s, 9H), 0.12, 0.10 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 173.7, 75.3, 65.0, 62.6, 59.0, 41.5, 30.7, 29.9, 26.8, 25.8, 23.0, 19.9, 19.1, 18.1, 13.6, −4.3, −4.6. Anal. Calcd for $C_{19}H_{36}O_4Si$: C, 64.00; H, 10.18. Found: C, 64.16; H, 10.18.

(32) Berque, I.; Le Ménez, P.; Razon, P.; Mahuteau, J.; Férézou, J.-P.; Pancrazi, A.; Ardisson, J.; Brion, J.-D. *J. Org. Chem.* **1999**, *64*, 373.

(2*R,3*S**,4*S**)-1-[4-(*tert*-Butyldimethylsiloxy)-3,6,6-trimethyltetrahydropyran-2-yl]methyl ketone (10*cis*).** To a degassed solution of 100 mg (0.34 mmol) of ketone **9** and 180 μL (0.67 mmol, 2.0 equiv) of Bu_3SnH in 3.4 mL of toluene at reflux was added a degassed solution of 460 μL (1.71 mmol, 5.0 equiv) of Bu_3SnH and 14 mg (0.85 mmol, 2.5 equiv) of AIBN in 4 mL of toluene, via syringe pump over 4 h. After refluxing an additional 30 min, the reaction mixture was cooled to 20 °C, and to the whole were added 10 mL of water and 40 mL of ether. The layers were separated, and the aqueous phase was extracted with 5 mL of ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 5:95 to 20:80) gave in order of elution 85 mg (85%) of **10*cis*** and 11 mg (10%) of **10*trans***.

Major 10*cis* isomer: IR (film) ν 2955, 1718, 1472, 1354, 1253, 1095 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.03 (td, 1H, J = 5.0, 11.7 Hz), 4.00 (d, 1H, J = 2.5 Hz), 2.22−2.20 (m, 1H), 2.20 (s, 3H), 1.55 (dd, 1H, J = 12.0, 14.0 Hz),1.41 (dd, 1H, J = 4.8, 13.0 Hz), 1.32, 1.20 (2s, 6H), 0.89 (s, 9H), 0.79 (d, 3H, J = 7.4 Hz), 0.06, 0.05 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.8, 78.9, 73.5, 68.4, 40.1, 37.8, 31.6, 27.5, 26.0, 23.0, 18.2, 5.1, −4.6. MS (CI, NH_3) m/z 318 ($M + NH_4^+$), 301 ($M + H^+$). Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 63.52; H, 10.81.

Minor 10*trans* isomer: IR (film) ν 2959, 1719, 1462, 1259, 1089, 1035 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (d, 1H, J = 10.5 Hz), 3.94 (t, 1H, J = 2.9 Hz), 2.18 (s, 3H), 1.72, 1.62 (2dd, 2H, J = 2.9, 14.0 Hz), 1.60−1.58 (m, 1H), 1.37, 1.21 (2s, 6H), 0.92 (s, 9H), 0.80 (d, 3H, J = 6.9 Hz), 0.06, 0.05 (2s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.3, 78.0, 71.7, 69.6, 43.2, 36.7, 32.3, 25.8, 25.2, 17.9, 13.2, −4.6, −5.4. MS (CI, NH_3) m/z 318 ($M + NH_4^+$), 301($M + H^+$).

(1*R(2*R**(1*S**)))-1-{2[1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-3-methybutyl]cyclopropyl}methyl Ketone (11).** To a solution of 50 mg (0.17 mmol) of **9** in 8.5 mL of THF, 0.85 mL of HMPA, and 34 μL (5 equiv) of methanol under argon at −78 °C was added 8.5 mL (0.1 M THF, 5 equiv) of a solution of SmI_2. The reaction mixture was stirred at −78 °C for 15 min and treated with 2 mL of water. The resulting mixture was partitioned between 10 mL of water and 50 mL of ether. The layers were separated and the aqueous phase was extracted with 3 × 5 mL of ether. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 5:90 to 30:60) gave 15 mg (29%) of **11** as a colorless oil. IR (film) ν 3450, 2959, 1718, 1362, 1257, 1044 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.06 (td, 1H, J = 3.2, 10.1 Hz), 3.76 (br s, 1H), 2.41−2.24 (m, 3H), 2.14 (s, 1H), 1.67 (dd, 1H, J = 9.9, 14.1 Hz), 1.30 (dd, 1H, J = 3.2, 14.4 Hz), 1.23, 1.21 (2s, 6H), 0.92 (m, 1H), 0.91 (s, 9H), 0.17 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.6, 77.8, 73.6, 70.1, 47.3, 42.2, 34.6, 31.2, 28.7, 26.1, 18.2, 14.0, −3.4, −4.5. MS (CI, NH_3) m/z 301 ($M + H^+$), 285, 229, 172, 153.

(2*R,3*S**,4*S**)-[4-(*tert*-Butyldimethylsiloxy)-3,6,6-trimethyltetrahydropyran-2-yl]methanol (16*cis*).** To a solution of 160 mg (0.42 mmol) of xanthate **13** and 340 μL (1.3 mmol, 3.0 equiv) of Bu_3SnH in 42 mL of benzene at reflux was added 7 mg (0.04 mmol, 0.1 equiv) of AIBN. The reaction mixture was refluxed for 30 min and cooled to 20 °C. The solvent was evaporated in vacuo to give crude **14** as a colorless oil. This unpurified product was immediately dissolved in 16 mL of THF, cooled to −10 °C, and treated with 4.2 mL (4.2 mmol, 10 equiv) of 1 M BH_3·THF in THF. The reaction mixture was stirred at 20 °C for 2 h, treated with 10 mL of ethanol, 5 mL of 5 N aqueous NaOH, and 10 mL of 35% H_2O_2, and then stirred at 20 °C for 1 h. The mixture was extracted with 50 mL of ether and 3 × 50 mL of EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 10:90) gave in order of elution 80 mg (66% from **13**) of the desired alcohol **16*cis*** and 18 mg (15%) of alcohol **17**. **16*cis*:** IR (film) ν 3442, 2957, 2929, 2857, 1464, 1379, 1256, 1107, 1079 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.00 (td, 1H, J = 4.9, 11.7 Hz), 3.73−3.71 (m, 2H), 3.47−3.45 (m, 1H), 1.96 (dd, 1H, J = 2.3, 10.4 Hz), 1.77 (br quint, 1H, J = 6.2 Hz), 1.56 (t, 1H, J = 12.4 Hz), 1.42 (dd, 1H, J = 4.2, 12.2 Hz), 1.25, 1.22 (2s, 6H), 0.90 (s, 9H), 0.82 (d, 3H, J = 6.9 Hz), 0.06 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 74.0, 73.4, 70.3, 64.7, 41.8, 37.5, 34.0, 26.0, 23.8, 18.2, 14.3, −4.5. MS (CI, NH_3) m/z 306 ($M + NH_4^+$), 289 ($M + H^+$).

For analytical purposes, **16*cis*** was converted to the corresponding bis(silyl) ether as follows. To a 0 °C solution of 96 mg (0.33 mmol) of alcohol **16*cis*** and 80 μL (0.69 mmol, 2.1 equiv) of 2,6-lutidine in 1 mL of CH_2Cl_2 was added dropwise 83 μL (36 mmol, 1.1 equiv) of TBSOTf. The mixture was then allowed to warm to 20 °C for 30 min and partitioned between 10 mL of ether and 5 mL of water. After decantation and separation, the organic phase was washed with 3 × 2 mL of water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 0:100 to 5:95) gave 126 mg (95%) of the desired bis(silyl) ether as a colorless oil. IR (film) ν 2929, 2857, 1472, 1463, 1388, 1362, 1255, 1104, 1070, 1006 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 3.98 (td, 1H, J = 4.9,11.7 Hz), 3.65 (dt, 1H, J = 2.0, 6.0 Hz), 3.62 (dd, 1H, J = 6.0, 9.3 Hz), 3.52 (dd, 1H, J = 6.7, 9.2 Hz,), 1.92−1.90 (m, 1H), 1.53 (t, 1H, J = 12.3 Hz), 1.39 (dd, 1H, J = 4.7, 12.9 Hz), 1.21, 1.20 (2s, 6H), 0.89, 0.88 (2s, 18H), 0.80 (d, 3H, J = 6.9 Hz), 0.06, 0.05 (2s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.9, 69.0, 63.7, 40.7, 36.3, 31.7, 26.0, 23.5, 18.3, 18.3, 4.0, −4.0, −4.6, −5.0, −5.3. MS (CI, NH_3) m/z 420 ($M + NH_4^+$), 345, 306, 289, 271, 213. Anal. Calcd for $C_{21}H_{46}O_3Si_2$: C, 62.62; H, 11.92. Found: C, 62.88; H, 11.53.

Ethyl (2*S,3*S**,4*S**,5*R**,6*S**,8*R**,9*S**,10*R**)-4,10-Dihydroxy-8-isopropyl-3,5,9-trimethyl-1,7-dioxaspiro[5.5]-undecane-2-carboxylate (18*trans*).** To a solution of 407 mg (0.92 mmol) of alcohol **4** in 4 mL of CH_2Cl_2 at 0 °C were added 640 μL (4.6 mmol, 5 equiv) of triethylamine and 150 μL (1.1 mmol, 1.2 equiv) of (bromomethyl)dimethylsilyl chloride, followed by a catalytic amount of DMAP. The mixture was stirred for 30 min at 20 °C and then partitioned between 10 mL of ether and 2 mL of saturated aqueous $NaHCO_3$. After decantation and separation, the aqueous layer was extracted with 3 × 5 mL of ether. The combined organic phases were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo.

To a solution containing the preceding unpurified bromomethylsilyl ether and 866 μL (3.2 mmol, 3.5 equiv) of Bu_3SnH in 25 mL of benzene at reflux under argon during 10 min was added 8 mg (0.023 mmol, 0.05 equiv) of AIBN. The reaction mixture was stirred at reflux under argon for 30 min, and then 8 mg of AIBN was added again. After 30 min of reflux, the solution was cooled to 20 °C, and the solvent was evaporated in vacuo to furnish a 2:1 mixture of *trans*/*cis* isomers of the desired methylated product.

The preceding crude product was dissolved in 8 mL of DMF and added with 1.7 g (5.5 mmol, 6.0 equiv) of TBAF·$3H_2O$ before heating at exactly 65 °C for 2 h. The reaction mixture was cooled to 20 °C and partitioned between 50 mL of ether and 10 mL of 1 N HCl. The layers were separated, and the aqueous phase was extracted with 3 × 10 mL of EtOAc. The combined organic layers were washed with water and brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 30:70 to 100:0) gave in order of elution 95 mg (30% from **4**) of **18*trans*** and 44 mg (14%) of **18*cis***, as colorless oils.

18*trans*: IR (film) ν 3509, 2963, 1740, 1458, 1378, 1260, 1154, 1014 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 4.35−4.27 (m, 2H), 3.97 (d, 1H, J = 11.2 Hz), 3.87 (d, 1H, J = 9.8 Hz), 3.65−3.63 (m, 1H), 3.52 (td, 1H, J = 2.7, 9.8 Hz), 3.27 (dd, 1H, J = 2.0, 10.3 Hz), 2.18 (dd, 1H, J = 4.8, 12.7 Hz), 2.10−1.95 (m, 3H), 1.82 (d, 1H, J = 5.4 Hz,), 1.25−1.40 (m, 5H), 1.07 (d, 3H, J = 7.0 Hz), 1.04 (d, 3H, J = 7.0 Hz), 0.95, 0.90, 0.85 (3d, 9H, J = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 102.1, 79.0, 75.3, 71.7, 69.9, 61.0, 42.3, 42.2, 40.7, 31.8, 28.0, 21.2, 14.3, 14.2, 13.6, 12.9, 12.3. MS (CI, NH_3) m/z 362 ($M + NH_4^+$), 345 ($M + H^+$), 327, 309, 293, 281, 255, 237, 215.

(2*S,3*S**,4*S**,5*R**,6*S**,8*R**,9*S**,10*R**)-[4,10-*bis*(*tert*-Butyldimethylsiloxy)-8-isopropyl-3,5,9-trimethyl-1,7-**

dioxaspiro[5.5]undec-2-yl]methyl Ketone (20*trans*). To a degassed solution of 23 mg (0.042 mmol) of ketone **19** and 23 μL (0.084 mmol, 2.0 equiv) of Bu_3SnH in 0.6 mL of benzene at reflux was added a degassed solution of 57 μL (0.21 mmol, 5.0 equiv) of Bu_3SnH and 17 mg (0.105 mmol, 2.5 equiv) of AIBN in 1 mL of benzene, via syringe pump over 3 h. After cooling to 20 °C, the reaction mixture was treated with 1 mL of water and 5 mL of ether. The layers were separated, and the aqueous phase was extracted with 2 mL of ether. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 0:100 to 10:90) gave in order of elution 5 mg (22%) of **20*trans*** and 8 mg (35%) of starting material. IR (film) ν 2958, 2858, 1720, 1472, 1384, 1255, 1168, 1076, 1032 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 3.94 (d, 1H, J = 10.7 Hz), 3.62 (t, 1H, J = 2.9 Hz), 3.60 (dt, 1H, J = 4.7, 10.3 Hz), 3.07 (dd, 1H, J = 2.1, 10.3 Hz), 2.19 (s, 3H), 1.94 (dd, 1H, J = 4.8, 12.6 Hz), 1.95−1.82 (3m, 3H), 1.39−1.37 (m, 1H), 1.30 (dd, 1H, J = 10.8, 12.3 Hz), 1.05, 0.97 (2d, 6H, J = 6.8 Hz), 0.91, 0.89 (2s, 18H), 0.86, 0.84,0.81 (3d, 9H, J = 6.4 Hz), 0.07, 0.06 (2s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 207.3, 100.7, 77.8, 76.2, 75.6, 72.0, 43.1, 42.6, 41.1, 32.8, 28.7, 26.5, 26.1, 25.9, 20.7, 18.8, 18.4, 14.5, 14.4, 13.0, 12.8, −3.9, −4.4. MS (CI, NH_3) m/z 543 (M + H$^+$), 411(100%), 279, 245, 227. Anal. Calcd for $C_{29}H_{58}O_5Si_2$: C, 64.15; H, 10.77. Found: C, 64.34; H, 10.83.

(2*R,3*S**,4*S**,5*R**,6*S**,8*R**,9*S**,10*R**)-[4,10-*bis*(*tert*-Butyldimethylsiloxy)-8-isopropyl-3,5,9-trimethyl-1,7-dioxaspiro[5.5]undec-2-yl]methanol (22*cis*).** To a solution of 232 mg (0.374 mmol) of the methyl xanthate derived from **21** and 300 μL (1.12 mmol, 3 equiv) of Bu_3SnH in 38 mL of benzene at reflux under argon during 10 min was added 6 mg (0.04 mmol, 0.1 equiv) of AIBN. The reaction mixture was stirred at reflux under argon for 1 h then cooled to 20 °C and concentrated in vacuo to give an oily crude product.

To the above unpurified product in 15 mL of THF at 0 °C was added 3.6 mL (1 M THF, 3.8 mmol, 10 equiv) of BH_3·THF. After 2 h at 20 °C, 10 mL of EtOH, 5 mL of 5 N aqueous NaOH, and 10 mL of H_2O_2 (35wt %) were added dropwise. After 1 h, the mixture was extracted with 15 mL of ether and with 2 × 15 mL of EtOAc. The combined organic layers were washed with 3 × 10 mL of brine, then dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification by column chromatography on silica gel (ether/petroleum ether, 5:95 to 20:80) gave 177 mg (89% for two steps) of alcohol **22*cis*** as a colorless oil. IR (film) ν 3480, 2957, 1471, 1385, 1256, 1081, 1006 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (ddd, 1H, J = 10.8, 8.0, 3.1 Hz), 3.56−3.51 (2m, 2H), 3.50 (dd, 1H, J = 11.2, 4.6 Hz), 3.50−3.48 (m, 1H), 3.46 (dd, 1H, J = 10.5, 2.0 Hz), 2.01 (dd, 1H, J = 13.1, 4.1 Hz), 1.86 (heptd, 1H, J = 6.9, 1.9 Hz), 1.78−1.75 (2m, 2H), 1.41−1.39 (m, 1H), 1.37 (dd, 1H, J = 13.1, 10.7 Hz), 0.96 (d, 3H, J = 6.8 Hz), 0.91, 0.90 (2s, 18H), 0.89 (d, 3H, J = 6.8 Hz), 0.88 (d, 3H, J = 6.9 Hz), 0.85 (d, 3H, J = 7.0 Hz), 0.84 (d, 3H, J = 7.3 Hz), 0.09, 0,08, 0.06, 0.05 (4s, 12H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 101.7, 77.6, 74.1,73.9, 70.8, 64.5, 41.7, 41.3, 37.6, 33.4, 28.4, 26.0, 25.9, 20.6, 18.2, 18.1, 14.3, 14.3, 12.7, 12.5, −3.9, −4.1, −4.6, −4.7. MS (CI, NH_3) m/z 532 (M + H$^+$), 399, 299, 267, 168. Exact mass calcd for $C_{28}H_{59}O_5Si_2$: 531.3901. Found: 531.3903.

Acknowledgment. J.-C.P. thanks the M.E.N.R. for a fellowship. The CNRS (UMR 7652) and the Ecole Polytechnique are acknowledged for financial support.

Supporting Information Available: Experimental procedures and characterization data for **6**, **9**, **13**, **17**, bis(silyl) ethers derived from **18*cis*** and **18*trans***, methyl xanthate derived from **21** and correlation experiments for **18*trans*** and **18*cis***. This material is available free of charge via the Internet at http://pubs.acs.org.

JO016231L