Total Synthesis of 10-Deoxymethynolide, the Aglycon of the Macrolide Antibiotic 10-Deoxymethymycin

Ronaldo A. Pilli,[†,*] Carlos Kleber Z. de Andrade,[†] Carlos Roberto O. Souto,[†] and Armin de Meijere[‡]

Instituto de Química, Unicamp, Cx. Postal 6154, 13083-970 Campinas, SP Brasil and Institut für Organische Chemie, Georg-August Universität, Tammannstraβe 2, Göttingen, Germany

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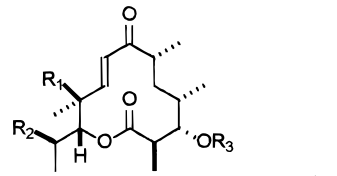
A short and efficient total synthesis of 10-deoxymethynolide (**2c**), the aglycon of 10-deoxymethymycin (**1c**), has been accomplished in 16 steps and 12% overall yield from (S)-3-*O*-*p*-toluenesulfonyl-3-hydroxy-2-methylpropanal (**15c**). The synthesis features an expeditious preparation of (+)-**5a**, a synthetic equivalent of the Prelog−Djerassi lactonic acid, and the construction of a 12-membered lactone through an intramolecular Nozaki−Hiyama−Kishi coupling reaction.

Introduction

The therapeutic properties and the complex architecture displayed by the polyoxomacrolide antibiotics have made them a highly valued family of synthetic targets.[1] Biogenetically oriented approaches toward their total syntheses based on the construction of a suitable seco-acid derivative, followed by its macrolactonization, have been explored.[2] The development of new methodologies for macrolactonizations[3] and asymmetric synthesis[2] and the discovery of new semisynthetic erythromycin A derivatives with better bioavailability and efficiency[4] have recently renewed the interest in the development of more efficient routes to this family of biologically active compounds.

The methymycin family of antibiotics comprises three 12-membered macrolides which have been isolated from *Streptomyces* species (methymycin **1a**,[5] neomethymycin **1b**,[5] and 10-deoxymethymycin **1c**[6]) which were shown to display antibiotic activity against Gram positive bacteria. Their structures have been established through chemical degradation,[6] spectroscopic studies,[7] and total synthesis.[8] Central to the earlier efforts in this area was the structural elucidation of the Prelog−Djerassi lactonic acid (**3**) which was first isolated as an oxidative degradation product of several macrolide antibiotics and emerged as a key building block in several total syntheses of this macrolide family.[9]



Methymycin (**1a**) was the first macrolide antibiotic to yield to total synthesis, and the Prelog−Djerassi lactonic acid (**3**) was used as the synthetic equivalent of the C_1−C_7 fragment of the natural product.[8] After that, several successful approaches to its aglycon **2a** and to the corresponding seco-acid followed[10,11] as well as reports by Yamaguchi et al. on the total synthesis of neomethynolide (**2b**), the aglycon of neomethymycin (**1b**).[12]

As to the synthetic efforts toward 10-deoxymethymycin (**1c**) or its aglycon **2c**, Ireland and co-workers described

* To whom correspondence should be addressed: Fax number: 55-19-7883023, e. mail: pilli@iqm.unicamp.br.

† Unicamp.

‡ Georg-August Universität.

(1) (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Omura, S., Ed. *Macrolide Antibiotics: Chemistry, Biology, and Practice*; Academic Press: Orlando, Fl, 1984.

(2) (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569. (b) Boeckman, R. H.; Goldstein, M. in *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1988; Vol. 7, p 1.

(3) Meng, Q.; Hesse, M. *Top. Curr. Chem.* **1991**, *161*, 107.

(4) (a) Lartley, P. A.; Nellans, H. N.; Tanaka, S. K. *Adv. Pharmacol.* **1994**, *28*, 307. (b) Kirst, H. A. in *Progress in Medicinal Chemistry*; Ellis, G. P.; Luscombe, D. K., Eds., Elsevier: New York, 1993; Vol. 30, p 57. (c) Jaynes, B. H.; Dirlam, J. P.; Hecker, S. J. in *Annual Reports in Medicinal Chemistry*; Bristol, J. A., Ed., Academic Press: New York, 1996; Vol. 31, p 31.

(5) (a) Djerassi, C.; Halpern, O. *J. Am. Chem. Soc.* **1957**, *79*, 2022. (b) Djerassi, C.; Halpern, O. *Tetrahedron* **1958**, *3*, 255.

(6) Kinumaki, A.; Suzuki, M. *J. Chem. Soc., Chem. Commun.* **1972**, 744.

(7) (a) Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1025. (b) Manwaring, D. G.; Rickards, R. W.; Smith, R. M. *Tetrahedron Lett.* **1970**, 1029.

(8) For the total synthesis of methymycin, see: (a) Masamune, S.; Kim, C. U.; Wilson, K. E.; Spessard, G. O.; Georghiou, P. E.; Bates, G. S. *J. Am. Chem. Soc.* **1975**, *97*, 3512. (b) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *J. Am. Chem. Soc.* **1975**, *97*, 3513.

(9) Martin, S. F.; Guinn, D. E. *Synthesis* **1991**, 245.

(10) For the total syntheses of methynolide (**2a**), see: (a) Nakano, A.; Takimoto, S.; Inanaga, J.; Katsuki, T.; Ouchida, S.; Inoue, K.; Aiga, M.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1019. (b) Inanaga, J.; Katsuki, T.; Takimoto, S.; Ouchida, S.; Inoue, K.; Nakano, A.; Okukado, N.; Yamaguchi, M. *Chem. Lett.* **1979**, 1021. (c) Tanaka, T.; Oikawa, Y.; Nakajima, N.; Hamda, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2203. (d) Oikawa, Y.; Tanaka, T.; Hamada, T.; Yonemitsu, O. *Chem. Pharm. Bull.* **1987**, *35*, 2202. (e) Oikawa, Y.; Tanaka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1986**, *27*, 3647. (f) Vedejs, E.; Buchanan, R. A.; Conrad, P.; Meier, G. P.; Mullins, M. J.; Watanabe, Y. *J. Am. Chem. Soc.* **1987,** *109*, 5878. **(**g) Vedejs, E.; Buchanan, R. A.; Watanabe, Y. *J. Am. Chem. Soc.* **1989**, *111*, 8430. (h) Ditrich, K. *Liebigs Ann. Chem.* **1990**, 789.

(11) For the total synthesis of protected forms of the methynolide seco-acid, see: (a) Grieco, P. A.; Ohfune, Y.; Yokoyama, Y.; Owens, W. *J. Am. Chem. Soc.* **1979**, *101*, 4749. (b) Ireland, R. E.; Daub, J. P.; Mandel, G. S.; Mandel, N. S. *J. Org. Chem.* **1983**, *48*, 1312.

(12) For the total synthesis of neomethynolide (**2b**), see: (a) Inanaga, J.; Kawamani, Y.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 1521. (b) Inanaga, J.; Kawamani, Y.; Yamaguchi, M. *Chem. Lett.* **1981**, 1415.

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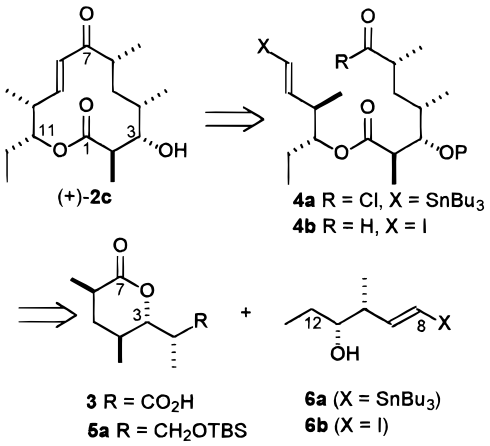
Scheme 1



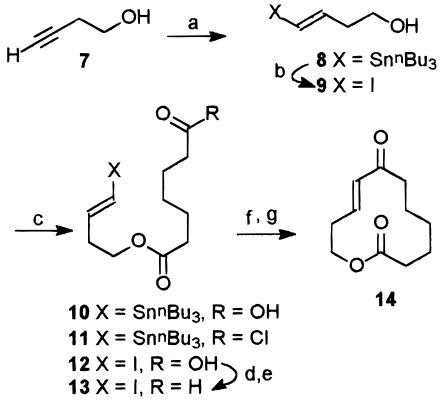
the total synthesis of the 3-OTBS derivative of 10-deoxymethynolide from D-glucose[11b] (23 steps and less than 1% overall yield), and Yamaguchi et al. reported on the total synthesis of 10-deoxymethynolide (**2c**),[13] in 12 steps and less than 0.1% overall yield from methyl (2*S*, 3*R*)-2,3-epoxybutanoate and the methyl ester of the Prelog−Djerassi lactonic acid (**3**), prepared via a nonstereoselective route from *cis*-2,4-dimethylglutaric anhydride.

Taking into account that the previous approaches to this family of macrolides have generally relied on a low yield esterification/lactonization strategy to construct the macrolide core, we considered a novel strategy to 10-deoxymethynolide (**2c**) based on the formation of the C(7)−C(8) bond as the final maneuver in the formation of the macrocycle. The ultimate precursor **4a** or **4b**, containing all the carbon atoms and stereochemical elements required for 10-deoxymethynolide (**2c**), was planned to undergo an intramolecular Stille coupling reaction or an intramolecular Nozaki−Hiyama−Kishi reaction, respectively, to provide a protected form of 10-deoxymethynolide (**2c**). Access to these advanced synthetic intermediates would be provided by *δ*-lactone **5a**, a synthetic equivalent of the Prelog−Djerassi lactonic acid (**3**), which we planned to prepare in a reduced number of steps via a combination of an enantioselective aldol condensation to set the proper configuration at C-2 and C-3 and an intramolecular alkylation step. Accordingly, vinylic stannane **6a** or vinylic iodide **6b** would also be provided by a short sequence involving an enantioselective aldol reaction to establish the stereogenic centers at C-10 and C-11 (Scheme 1).

Results and Discussion

To validate the construction of the dodecanolide ring system through a carbon−carbon bond-forming approach, we first examined the preparation of the model compounds **11** and **13** (Scheme 2). The corresponding carboxylic acids **10** and **12** were readily assembled as depicted in Scheme 2. However, all attempts to convert carboxylic acid **10** to the corresponding acyl chloride **11** failed, even when the protocol described by Baldwin et al. to prepare *β*-stannylalkenoates containing an acyl

Scheme 2[a]



[a] (a) $^{n}Bu_3SnH$, AIBN (cat.), 80 °C (80%); (b) I_2, CCl_4, rt (85%); (c) pimelic acid, DCC, DMAP(cat.), CH_2Cl_2, rt (62% for **10**; 79% for **12**); (d) (i) $(COCl)_2$, DMF(cat.), CH_2Cl_2; 0 °C; (ii) **12**, THF, CH_3CN, C_5H_5N, −30 °C; (e) $LiAlH(O^tBu)_3$, CuI (10 mol %), THF, −78 °C (51%, two steps); (f) $CrCl_2$ (9 equiv), $NiCl_2$ (0.09 equiv), DMF(7.5×10^{-3} M), rt (63%); (g) PDC, CH_2Cl_2 (75%).

chloride functionality was employed[14] or when the potassium salt from **10** was used. Protodestannation prevailed and forced us to explore the Nozaki−Hiyama−Kishi coupling.

Vinylic iodide **9** was readily prepared from vinylic stannane **8** and esterified with pimelic acid. After conversion of the carboxylic acid to the corresponding acyl chloride and reduction with $LiAlH(O^tBu)_3$, aldehyde **13** smoothly underwent intramolecular Nozaki−Hiyama−Kishi coupling reaction when treated with an excess of $CrCl_2$ (9 equiv) containing 1 mol % of $NiCl_2$ in degassed DMF (7.5×10^{-3} M). The corresponding allylic alcohol was isolated in 63% yield and oxidized with PDC in CH_2Cl_2 to provide **14**, in 75% yield.

Having selected an attractive methodology to construct a 12-membered lactone ring, a convergent and efficient route to **4b** still had to be accomplished. This naturally led us to consider the preparation of *δ*-lactone **5a**, a synthetic equivalent of the Prelog−Djerassi lactonic acid, and vinylic iodide **6b** in their enantiomerically pure forms through enantioselective aldol condensation.[16]

At the outset we were attracted by the possibility of construction of the *δ*-lactone ring required in **5a** through an intramolecular alkylation process which builds upon the stereochemical and the structural platform provided by the preceding enantioselective aldol condensation step. We and others[17] have previously turned this synthetic plan into practice. Although in the present case we were

(13) Inanaga, J.; Kawamani, Y.; Sakata, I.; Okukado, M.; Yamaguchi, M. 24th Symposium on the Chemistry of Natural Products, Osaka, Japan, 1981; Hashiwa Publ. Co. Nagoya, Japan, 1961; pp 654−661.

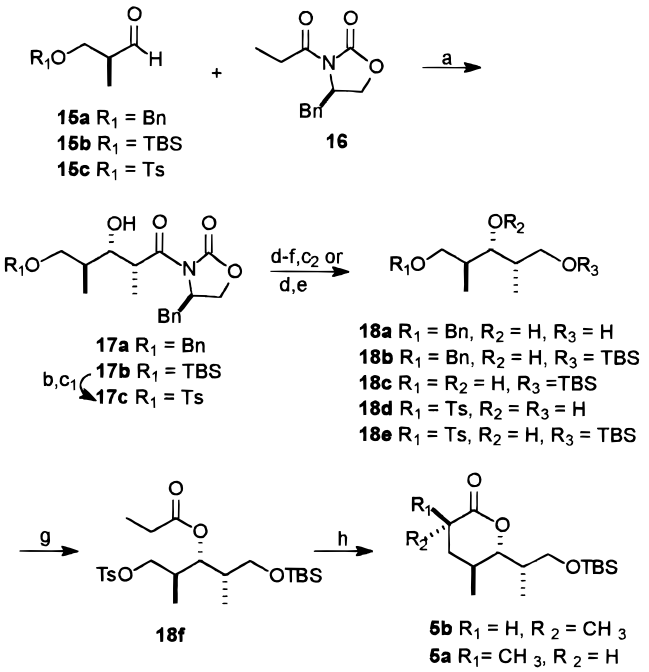
(14) Baldwin, J. E.; Adlington, R. M.; Ramcharitar, S. H. *Tetrahedron* **1992**, *48*, 2957.

(15) (a) Cintas, P. *Synthesis* **1992,** 248. (b) Kishi, Y. *Pure Appl. Chem*. **1992,** *64*, 343. For examples of the use of the intramolecular version, see: (c) Schreiber, S. L.; Meyers, H. V. *J. Am. Chem. Soc.* **1988**, *110*, 5198. (d) Aoyagi, S.; Wang, T.-C.; Kibayashi, C. *J. Am. Chem. Soc.* **1993**, *115*, 11393. (e) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. (f) Harwig, C. W.; Py, S.; Fallis, A. G. *J. Org. Chem*. **1997**, *62*, 7902.

(16) Kim, B. M.; Williams, S. F.; Masamune, S. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds. Pergamon Press: New York, 1991; Vol. 2, p 239.

(17) For the preparation of *δ*-lactones through the intramolecular alkylation of ester enolates, see: (a) Pilli, R. A.; Murta, M. M. *J. Org. Chem*. **1993**, *58*, 338. (b) White, J. D.; Amedio, J. C., Jr.; Gut, S.; Ohira, S.; Jayasinghe, L. R. *J. Org. Chem*. **1992**, *57*, 2270. (c) Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. *Tetrahedron* **1990**, *46*, 3469. (d) Nakai, E.; Kitahara, E.; Sayo, N.; Ueno, Y.; Nakai, T. *Chem. Lett*. **1985**, 1725.

Scheme 3[a]



[a] (a) (i) Bu_2BOTf, CH_2Cl_2, DIPEA, 0 °C; (ii) **15a** or **15b** or **15c**, −78 °C; (iii) H_2O_2, MeOH, 0 °C (**17a**, 89%, **17b**, 79%, **17c**, 73%); (b) HF, CH_3CN, H_2O, rt; (c) TsCl, Et_3N, DMAP(cat.), CH_2Cl_2, 0 °C (c_1: 81%, two steps, for **17c**; c_2: 100% for **18e**); (d) $LiBH_4$, MeOH, THF, 0 °C; (e) TBDMSCl, Et_3N, DMAP(cat.), CH_2Cl_2, rt (80% from **17a**; 91% from **17c**); (f) H_2, Pd/C, EtOH (78%); (g) $(CH_3CH_2CO)_2O$, Et_3N, DMAP(cat.), CH_2Cl_2 (95%); (h) (i) *tert*-BuOK, THF, rt; (ii) *tert*-BuOK, *tert*-BuOH, rt (62%).

not sure about the stereochemical outcome at C-6, we were confident that the thermodynamically favored cis configuration of the methyl groups at C-4 and C-6 in **5a** would be properly established after equilibration under basic conditions of an epimeric mixture at C-6 eventually obtained after the intramolecular alkylation step.[18]

Initially, the preparation of the required tosyl derivative **18e** was envisaged from **17a**, based on the known preference for the *syn*,*anti*-Felkin stereochemistry in the aldol adduct obtained from (+)-**15a** and the boron enolate of (*R*)-4-benzyl-3-propionyl-2-oxazolidinone (**16**) (Scheme 3). Indeed, the reaction of the boron enolate of imide (+)-**16**[20] and aldehyde **15a**[19] afforded aldol (−)-**17a** in 89% yield after purification by flash chromatography. The *syn*,*anti*-stereochemistry of (−)-**17a** was established after its $LiBH_4$ reduction to afford known diol **18a**[17a,21] which required careful purification by flash chromatography on silica gel to be separated from (*R*)-4-benzyl-2-oxazolidinone. Preparatively, the crude mixture of **18a** and oxazolidinone was silylated (TBDMSCl, Et_3N, cat. DMAP, CH_2Cl_2), and alcohol (+)-**18b** (80% overall yield) was readily separated from the recovered chiral auxiliary (80% yield) by column chromatography.

Alcohol (+)-**18b** was transformed into the tosyl derivative (−)-**18e** after hydrogenolysis and tosylation (78% overall yield). Most of the reaction conditions previously described for the intramolecular alkylation of ester enolates failed[17b−d] when applied to (−)-**18f**. However, treatment of (−)-**18f** with freshly sublimed *tert*-BuOK (4 equiv) in THF (0 °C to room temperature) afforded a 2:1 mixture of epimeric lactones **5a**/**5b** (68% yield). Under equilibrating conditions (*tert*-BuOK/*tert*-BuOH, rt) this ratio could be improved to 10:1 in favor of (+)-**5a**.[18]

The success of the lactonization and equilibration steps led us to consider a more direct route to (−)-**18e** which required the preparation of *O*-tosyl aldehyde **15c**. Attempts to carry out the reduction of methyl (*S*)-3-*O*-(*p*-toluenesulfonyl)-3-hydroxy-2-methylpropionate with DIBAL in CH_2Cl_2 at −78 °C led to the formation of **15c** in low yield together with the corresponding alcohol.[22] When the reaction was carried out in toluene and the temperature of the cooling bath (liquid N_2/hexanes) carefully controlled below −90 °C, overreduction was suppressed. Isolated crude aldehyde **15c** was shown to be pure enough by ^1H NMR spectroscopy to be used in the next step without further purification.

The di-*n*-butyl boron triflate/diisopropylethylamine reaction conditions were sufficiently mild to allow us to carry out the desired aldol condensation of the base sensitive aldehyde **15c** with the boron enolate of imide (+)-**16**. Stereochemically homogeneous aldol (−)-**17c** was isolated in 73% overall yield, as judged by its ^1H NMR spectrum (300 MHz).

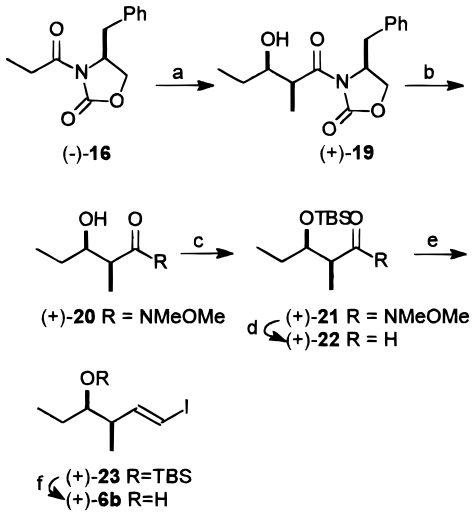
The *syn*,*anti*-Felkin stereochemistry of (−)-**17c** was assigned after comparison with an authentic sample prepared from (−)-**17b**:[23] desilylation of (−)-**17b** (HF/CH_3CN/H_2O) followed by tosylation of the primary alcohol (TsCl, Et_3N, CH_2Cl_2, DMAP) afforded (−)-**17c** in 81% yield. Reduction of (−)-**17c** with $LiBH_4$ and protection of the primary alcohol with TBDMSCl afforded (−)-**18e** (91% overall yield) and recovered (*R*)-4-benzyl-2-oxazolidinone (83% yield), after purification by column chromatography. Propionylation of (−)-**18e** afforded (−)-**18f** (95% yield), and intramolecular alkylation, as described above, was followed by equilibration in *tert*-BuOK/*tert*-BuOH to afford (+)-**5a** in 62% yield.

After developing a short and efficient preparation of the C-1/C-7 fragment (+)-**5a** (five steps, 39% overall yield from **15c**), we moved to the preparation of the required vinylic iodide (+)-**6b**: the enantioselective aldol condensation of the boron enolate derived from (−)-**16** and propionaldehyde afforded diastereomerically pure (+)-**19**[24] (77% yield) which was uneventfully converted to aldehyde (+)-**22**. Vinylic iodide (+)-**6b** was prepared as a 18:1 mixture of *E*:*Z* isomers from (+)-**22** following the olefination procedure developed by Takai and co-workers (Scheme 4).[25]

The coupling of the C(1)−C(7) and C(8)−C(13) fragments required some previous functional group manipulations in order to adjust the requisite oxidation states at C-1 and C-7 carbon atoms of (+)-**5a** (Scheme 5). Although several scenarios could be envisioned for the

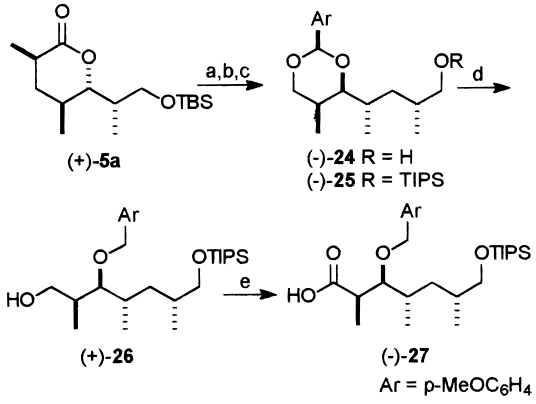
(18) Suzuki, K.; Tomooka, K.; Katayama, E.; Matsumoto, T.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1986**, *108*, 5221.
(19) Jackson, R. F. W.; Sutter, M. A.; Seebach, D. *Liebigs Ann. Chem.* **1985**, 2313.
(20) Gage, J. R.; Evans, D. A. *Organic Synthesis*; Wiley: New York, 1993; Collect. Vol. VIII, p 339.
(21) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
(22) The DIBAL-H reduction of methyl (*R*)-*O*-*p*-toluenesulfonyl-3-hydroxy-2-methylpropionate in CH_2Cl_2 has been previously described: van Maarseveen, J. H.; Scheeren, H. W. *Tetrahedron* **1993**, *49*, 2325.
(23) The preparation of (+)-**17b** has been previously described: Clark, D. L.; Heathcock, C. H. *J. Org. Chem.* **1993**, *58*, 5878. We thank the authors for a copy of its ^1H NMR spectrum.
(24) For the preparation of (−)-**19**, see: Chan, P. C−M.; Chong, J. M.; Kousha, K. *Tetrahedron* **1994**, *50*, 2703.
(25) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.

Scheme 4[a]



[a] (a) (i) $^{n}Bu_2BOTf$, DIPEA, CH_2Cl_2, 0 °C; (ii) C_2H_5CHO, −78 °C (77%); (b) $AlMe_3$, MeONHMe·HCl (93%); (c) TBDMSCl, DMF, imidazole (76%); (d) DIBAL-H, toluene, −78 °C (78%); (e) $CrCl_2$ (6 equiv), CHI_3 (2 equiv), THF, rt (59%); (f) HF, CH_3CN, H_2O, rt (94%).

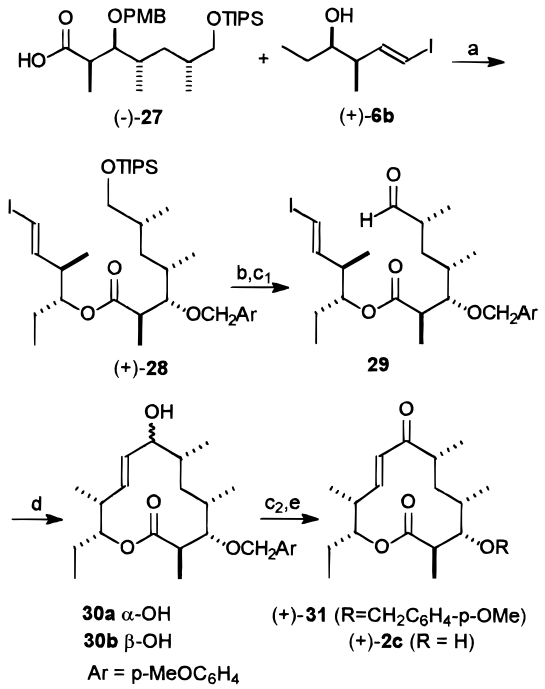
Scheme 5[a]



[a] (a) $LiAlH_4$, THF, rt (94%); (b) *p*-$MeOC_6H_4CH(OMe)_2$, CH_2Cl_2, CSA(cat.), rt (98%); (c) TIPSCl, DMF, imidazole (100%); (d) DIBAL-H, toluene, 0 °C (99%); (e) CrO_3, H_2SO_4, acetone, rt (71%).

conversion of (+)-**5a** to (−)-**27**, this was efficiently carried out through the intervention of *p*-methoxybenzylidene-acetal (−)-**25**, readily prepared by $LiAlH_4$ reduction of (+)-**5a**, reaction with *p*-methoxybenzylidene dimethyl-acetal and protection of the primary hydroxyl group (92% overall yield). When (−)-**25** was treated with DIBAL-H in toluene at 0 °C, a regioselective reductive ring opening of the 1,3-dioxane ring took place from the sterically less congested carbinolic position,[26] thus allowing differentiation of the two primary alcohols at C(1) and C(7) and the secondary one at C(3) which remained protected as the corresponding *p*-methoxybenzyl ether. Jones oxidation of (+)-**26** afforded carboxylic acid (−)-**27** (71% yield) which was esterified with alcohol (+)-**6b** under the conditions developed by Yamaguchi and co-workers (97% yield).[27]

Scheme 6[a]



[a] (a) 2,4,6-Trichlorobenzoyl chloride, Et_3N, THF; then (+)-**6b** (97%); (b) HF, CH_3CN, H_2O, rt (94%); (c) Dess−Martin periodinane (c_1: 100% and c_2: 77%); (d) $CrCl_2$ (20 equiv), $NiCl_2$ (0.2 equiv), DMF, rt (74%); (e) DDQ, CH_2Cl_2, H_2O (96%).

Deprotection of (+)-**28** followed by oxidation with Dess−Martin periodinane set the stage for the key step in the synthetic scheme: when crude aldehyde **29** was treated with excess of $CrCl_2$ (10 equiv)[28] containing 1% of $NiCl_2$, a smooth reaction ensued to afford a 1:1 mixture of diastereoisomeric allylic alcohols **30a**/**30b**, in 74% yield (Scheme 6).[29] As the stereochemistry at C-7 was of no consequence for the total synthesis of 10-deoxymethynolide (**2c**), the epimeric mixture of **30a**/**30b** was oxidized with Dess−Martin periodinane to afford (+)-**31** followed by deprotection of the secondary alcohol upon treatment with DDQ. Synthetic (+)-10-deoxymethynolide (**2c**), obtained in 74% yield after two steps, displayed spectroscopic data (^1H and ^{13}C NMR) identical to those reported by Lambalot and Cane for 10-deoxymethynolide produced by *S. venezuelae*.[30]

In conclusion, a short preparation of (+)-**5a**, a synthetic equivalent of the Prelog−Djerassi lactonic acid in five steps and 39% overall yield has been developed employing an enantioselective aldol reaction of a chiral *β*-tosyloxy aldehyde. This intermediate was converted in 11 steps and 32% yield to (+)-10-deoxymethynolide (**2c**), the aglycon of 10-deoxymethymycin, featuring an efficient construction of the 12-membered macrolactone ring through an intramolecular Nozaki−Hiyama−Kishi coupling reaction. Studies are underway aimed at control-

(26) (a) Takano, S.; Akiyama, M.; Sato, S.; Ogasawara, K. *Chem. Lett.* **1983**, 1593. (b) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446.

(27) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

(28) The Nozaki−Hiyama−Kishi coupling experiments were carried out with $CrCl_2$ purchased from Merck Schuchardt and dried at 1 mmHg and 250 °C for 8 h immediately prior to use.

(29) The stereochemical assignment at C(7) of epimeric alcohols **30a** (more polar) and **30b** (less polar) rests solely on the analysis of their ^1H NMR spectra assuming a Celmer type conformation of the 12-membered lactone: H-7 in less polar isomer **30b** appeared as a double doublet at δ 4.15 ppm and coupling constants of 10.0 and 5.0 Hz consistent with a trans-diaxial relationship for H-7 and H-6 while in the more polar isomer **30a** the corresponding signal is a broad singlet.

(30) Lambalot, R. H.; Cane, D. E. *J. Antibiot.* **1992**, *45*, 1981.

ling the stereochemical outcome of this reaction as applied to the formation of medium- and large-ring lactones.

Experimental Section

General. Unless otherwise noted materials were obtained from commercial suppliers and were used without further purification. THF and ether were distilled from sodium−benzophenone ketyl prior to use. Diisopropylamine, diisopropylethylamine, triethylamine, dichloromethane, and *N*,*N*-dimethylformamide were distilled from calcium hydride. $^{n}Bu_2BOTf$ was prepared according to ref 20 and distilled immediately prior to use. Potassium *tert*-butoxide was sublimed prior to use, and $CrCl_2$ containing 1 mol % of $NiCl_2$ was activated 8 h at 250 °C in a vacuum (1 mmHg) and weighed under argon atmosphere in a glovebox. All the reactions involving organometallic reagents, metallic hydrides and $^{n}Bu_2BOTf$ were carried out under an argon atmosphere with heat-dried glassware. The normal processing of organic extracts consisted of drying over $MgSO_4$, filtration, and concentration with a rotary evaporator at 40 mmHg. Melting points are uncorrected and ^{1}H NMR spectra were recorded in $CDCl_3$ solution at 300 MHz and ^{13}C NMR spectra at 75.2 MHz, unless otherwise noted. *J* values are given in hertz.

(*E*)-1-(Tri-*n*-butylstannyl)-1-buten-4-ol (8). A mixture of 3-butyn-1-ol (1.17 g 16.7 mmol), tributyltin hydride (7.30 g, 25.0 mmol), and AIBN (0.085 g, 0.52 mmol) was heated 16 h in an oil bath at 90−100 °C. The crude mixture of the (*E*:*Z*)-**8** was purified by flash chromatography (5% ethyl acetate−pentane) to afford 4.82 g (13.4 mmol) of (*E*)-**8** (80% yield). IR (film, NaCl): 3400 (br), 2960, 2984, 980 cm^{-1}; ^{1}H NMR (250 MHz): δ 0.8−1.0 (m, 15H), 1.2−1.4 (m, 6H), 1.4−1.6 (m, 6H), 2.42 (q, 2H, J = 6.9), 3.6−3.7 (m, 2H), 5.95 (dt, 1H, J = 6.8 and 18.9), 6.05 (d, 1H, J = 18.9); ^{13}C NMR (62.5 MHz): 9.4, 13.7, 27.3, 29.1, 41.2, 61.4, 132.1, 144.8.

(*E*)-4-Iodo-3-buten-1-ol (9). To a solution of alcohol **8** (0.97 g, 2.7 mmol) in CCl_4 (10 mL) was added resublimed iodine (1.70 g, 6.70 mmol), and the mixture was stirred 1 h at room temperature when it was treated with 10% aq $NaHSO_3$ (10 mL) and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (15 mL) and processed. The crude product was purified by flash chromatography (5% ethyl acetate−pentane) to yield 0.46 g of vinylic iodide **9** (2.3 mmol, 85% yield). IR (film, NaCl): 3410 (br), 3060, 2975, 1632, 1100 cm^{-1}; ^{1}H NMR (250 MHz): δ 2.10 (s, br, 1H), 2.32 (q, 2H, J = 6.4), 3.63 (t, 2H, J = 6.4), 6.20 (d, 1H, J = 14.7), 6.54 (dt, 1H, J = 14.7 and 7.3); ^{13}C NMR (62.5 MHz): δ 39.0, 60.8, 77.0, 142.6.

(*E*)-4-(Tri-*n*-butylstannyl)-3-butenyl Pimelate (10). A solution of pimelic acid (0.57 g, 3.6 mmol) in CH_2Cl_2 (16.5 mL) was treated with a solution of DMAP (0.13 g, 1.1 mmol) and DCC (0.73 g, 3.5 mmol) in CH_2Cl_2 (7.0 mL). The mixture was stirred 30 min at room temperature when a white precipitate was formed. To this mixture was added dropwise a solution of **8** (0.86 g, 2.4 mmol) in CH_2Cl_2 (4.8 mL), and the mixture was stirred 2 h at room temperature. The solids were filtered off and washed with CH_2Cl_2 (40 mL), and the organic layers were combined and processed. The crude mixture was purified by column chromatography (20% ethyl acetate−pentane) to afford 0.78 g (1.5 mmol, 62% yield) of ester **10**. IR (film, NaCl): 3350−2500 (br), 2926 (br), 1739, 1710, 1174 cm^{-1}; ^{1}H NMR (250 MHz): δ 0.8−1.0 (m, 15H), 1.2−1.8 (m, 18H), 2.3−2.5 (m, 6H), 4.10 (t, 2H, J = 7.3), 5.92 (dt, 1H, J = 19.6 and 4.9), 6.00 (d, 1H, J = 19.6), 10.51 (s, br, 1H); ^{13}C NMR (62.5 MHz): δ 9.3, 13.5, 24.2, 24.4, 27.1, 28.9, 29.0, 33.7, 33.9, 36.8, 63.4, 131.2, 143.7, 173.5, 179.3.

(*E*)-4-Iodobuten-3-yl Pimelate (12). The same procedure as described above afforded ester **12**, in 79% yield. IR (film, NaCl): 3400−2600 (br), 1735, 1710, 1125 cm^{-1}; ^{1}H NMR (250 MHz): δ 1.3−1.5 (m, 2H), 1.5−1.8 (m, 4H), 2.2−2.4 (m, 6H), 4.12 (t, 2H, J = 7.0), 6.14 (d, 1H, J = 15.0), 6.51 (dt, 1H, J = 7.3 and 14.7).

(*E*)-4-Iodobuten-3-yl 6-Formylhexanoate (13). To a mixture of DMF (0.030 mL, 0.39 mmol) and CH_2Cl_2 (0.6 mL) at 0 °C was added oxalyl chloride (0.10 mL, 0.14 g, 1.1 mmol) dropwise. After 1 h, the volatiles were removed under vacuum (0.1 mmHg), and CH_3CN (0.6 mL) and THF (0.1 mL) were added to the white solid residue. The suspension was cooled to −30 °C, and a solution of **12** (0.14 g, 0.43 mmol) and pyridine (0.030 mL, 0.37 mmol) in THF (0.6 mL) was added dropwise. After 1 h at −30 °C, CuI (0.0071 g, 0.037 mmol) was added, the mixture was cooled to −78 °C, and a solution of $LiAlH(O^tBu)_3$ (0.21 g, 0.82 mmol) in THF (1.0 mL) was added. The reaction mixture was stirred 30 min at −78 °C, quenched with 2 N HCl (1.0 mL), and extracted with ether (3 × 5 mL). The combined organic layers were washed with satd $NaHCO_3$ (10 mL) and processed. Purification of the residue by flash chromatography (5% ethyl acetate−pentane) afforded 0.070 g of aldehyde **13** (0.22 mmol, 51% yield). IR: 2975, 1720, 1735; ^{1}H NMR (250 MHz): δ 1.3−1.4 (m, 2H), 1.6−1.8 (m, 4H), 2.31 (t, 2H, J = 7.0), 2.35−1.50 (m, 4H), 4.12 (t, 2H, J = 7.0), 6.23 (d, 1H, J = 14.4), 6.50 (dt, 1H, J = 14.4 and 7.2), 9.81 (t, 1H, J = 1.6); ^{13}C NMR (62.5 MHz): δ 21.6, 24.5, 28.4, 33.8, 35.1, 43.5, 62.1, 77.3, 141.6, 173.2, 202.3.

(*E*)-7-Oxo-8-dodecenolide (14). To a suspension of anhydrous $CrCl_2$ containing 1 mol % of $NiCl_2$ (0.35 g, 2.8 mmol) in degassed DMF (34 mL) was added a solution of aldehyde **13** (0.10 g, 0.31 mmol) in degassed DMF (6.0 mL), and the reaction mixture was stirred 2 h at room temperature and under an argon atmosphere. The reaction mixture was poured into water (10 mL) and extracted with ether (3 × 15 mL). The organic layers were combined and normally processed, and the residue was dissolved in CH_2Cl_2 (2.0 mL) and treated with PDC (0.25 g, 0.66 mmol), anhydrous $MgSO_4$ (0.050 g, 0.42 mmol) and Celite (0.050 g). The reaction mixture was stirred 14 h at room temperature and, filtered through a Celite pad, and the solvent was removed under reduced pressure. Purification of the crude product by flash chromatography (10% ethyl acetate−pentane) afforded lactone **14** (0.029 g, 0.15 mmol), in 47% yield (mp 76−77 °C). IR (KBr): 2960, 2870, 1721, 1691,1630, 1150 cm^{-1}; ^{1}H NMR (C_6D_6, 500 MHz): δ 1.02−1.06 (m, 2H), 1.20−1.26 (m, 2H), 1.29−1.36 (m, 2H), 1.69−1.74 (m, 2H), 2.00−2.04 (m, 2H), 2.07−2.10 (m, 2H), 3.83−3.86 (m, 2H), 5.91 (dt, 1H, J = 15.5 and 0.8), 6.28 (dt, 1H, J = 15.5 and 7.8); ^{13}C NMR: δ 23.5, 23.7, 24.7, 32.5, 32.7, 40.9, 60.3, 134.4, 139.5, 172.6, 202.2. MS (*m*/*z*): 41, 55, 81 (100%), 99, 196 ($M^{+\cdot}$), 197 ($M + 1^{+\cdot}$).

(4*R*)-*N*-[(2′*R*,3′*S*,4′*S*)-5′-*O*-Benzyl-2′,4′-dimethyl-3′,5′-dihydroxy-1′-oxopentyl]-4-benzyl-2-oxazolidinone (17a). To a 0.5 M soln of imide (+)-**16** (1.6 g, 6.9 mmol) in CH_2Cl_2, under an argon atmosphere at 0 °C, was added di-*n*-butylboron triflate (2.1 mL, 8.3 mmol) followed by diisopropylethylamine (1.6 mL, 9.0 mmol). After allowing 30 min for complete enolization, the reaction mixture was cooled to −78 °C, and aldehyde **15a**[19] (0.98 g, 5.5 mmol of 0.5 M soln in CH_2Cl_2) was added dropwise. Stirring was continued for 30 min at −78 °C, followed by 2.0 h at 0 °C. The reaction mixture was quenched with pH 7.0 phosphate buffer (6.0 mL) and methanol (18 mL). A solution of hydrogen peroxide (30% v/v, 6.0 mL) in methanol (12 mL) was added and the mixture allowed to stir for 1.0 h at 0 °C. The reaction mixture was diluted with Et_2O (50 mL) and successively washed with 5% aq $NaHCO_3$ (40 mL), 10% HCl (40 mL), and brine (40 mL). The organic layer was normally processed, and purification by column flash chromatography on silica gel (20% EtOAc in hexanes, v/v) afforded **17a** (2.0 g, 4.9 mmol), in 89% yield. $[\alpha]^{25}_D = -37.8$ (*c* 0.9, $CHCl_3$); IR (NaCl, film): 3490, 2970, 1779, 1697, 1210 cm^{-1}. ^{1}H NMR: δ 0.96 (d, 3H, J = 7.0), 1.26 (d, 3H, J = 6.7), 1.92−2.06 (m, 1H), 2.76 (dd, 1H, J = 13.3 and 9.9), 3.31 (dd, 1H, J = 13.3 and 3.0), 3.50−3.65 (m, 2H), 3.85−4.00 (m, 2H), 4.16 (d, 2H, J = 5.4 Hz), 4.51 (s, 2H), 4.61−4.70 (m, 1H), 7.2−7.4 (m, 10H); ^{13}C NMR (75.5 MHz): δ 9.5, 13.4, 35.9, 37.6, 40.5,55.5, 66.1, 73.4, 74.8, 75.2, 127.4, 127.7, 127.8, 128.5, 129.0, 129.5, 135.4, 137.8, 153.2, 176.3. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.37; H, 7,01; N, 3.26.

(*S*)-*O*-*p*-Toluenesulfonyl-3-hydroxy-2-methylpropanal (15c). To a soln of methyl (*S*)-*O*-*p*-toluenesulfonyl-3-hydroxy-2-methylpropionate[11] (0.65 g, 2.4 mmol) in toluene at

−95 °C (liquid N_2/hexanes bath) was added dropwise (ca. 0.8 mL min^{-1}) a 1.0 M soln of DIBAL in toluene (3.1 mL, 3.1 mmol). The reaction mixture was stirred 1.5 h at −95 °C, quenched with ethyl acetate (3.0 mL), followed by addition of Et_2O (20 mL) and satd soln of sodium and potassium tartrate (1.5 mL). The reaction mixture was allowed to warm to room temperature, and stirring was continued until phase separation. The organic layer was separated, the aqueous one was further extracted with Et_2O (2 × 20 mL), the combined organic layers were concentrated under reduced pressure, and the residue was filtered through Celite. Evaporation under reduced pressure afforded crude **15c** (0.50 g) which was used in the next step without further purification. IR (film, NaCl): 2979, 1735, 1359, 1177 cm^{-1}; ^1H NMR: δ 1.16 (d, 3H, J = 7.3), 2.46 (s, 3H), 2.70−2.80 (m, 1H), 4.15 (dd, 1H, J = 9.9 and 5.5), 4.25 (dd, 1H, J = 9.9 and 6.1), 7.36 (d, 2H, J = 8.1), 7.78 (d, 2H, J = 8.1), 9.60 (s, 1H); ^{13}C NMR: δ 10.5, 21.6, 45.5, 68.9, 127.9, 129.8, 129.9, 145.1, 200.7.

(4*R*)-*N*-[(2′*R*,3′*S*,4′*S*)-2′,4′-Dimethyl-3′-hydroxy-5′-*O*-*p*-toluenesulfonyl-1′-oxopentyl]-4-benzyl-2-oxazolidinone (17c). (a) From 15c: The same procedure described above for **17a** afforded **17c** (0.88 g, 1.9 mmol, 73% yield) as a colorless oil from imide (+)-**16** (0.72 g, 3.1 mmol) and aldehyde **15c** (0.62 g, 2.6 mmol) after purification by flash chromatography on silica gel (35% ethyl acetate/hexanes). $[\alpha]^{25}_D = -27.7$ (*c* 2.5, $CHCl_3$); IR (film, NaCl): 3500 (br), 2982, 1782, 1700, 1400, 1355, 1181 cm^{-1}; ^1H NMR: δ 0.94 (d, 3H, J = 6.9), 1.21 (d, 3H, J = 6.9), 1.9−2.0 (m, 1H), 2.44 (s, 3H), 2.79 (dd, br, 2H, J = 13.3 and 9.3), 3.22 (dd, 1H, J = 13.3 and 3.3), 3.78 (dd, 1H, J = 8.6 and 2.9), 3.85 (dq, 1H, J = 6.9 and 2.9), 4.10−4.31 (m, 4H), 4.67−4.73 (m, 1H), 7.20−7.35 (m, 7H), 7.78 (d, 2H, J = 8.3); ^{13}C NMR: δ 10.2, 13.3, 21.6, 35.6, 37.7, 39.2, 54.9, 66.2, 71.4, 72.4, 127.4, 127.9, 128.9, 129.4, 129.8, 132.8, 134.9, 144.6, 152.8, 177.4. Anal. Calcd for $C_{24}H_{29}NO_7S$: C, 60.61, H, 6.15, N, 2.94. Found: C, 60.25, H, 5.94, N, 2.75. **(b) From 17b:** To **17b** (0.52 g, 1.2 mmol), prepared according to ref 23, was added a soln (4.0 mL) of 15% HF (0.5 mL) in CH_3CN (8.6 mL) and water (0.9 mL). The reaction mixture was stirred 30 min at room temperature, diluted with Et_2O (30 mL), washed with brine (10 mL), and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (5.0 mL), and Et_3N (0.18 mL, 0.128 g, 1.27 mmol), DMAP (0.015 g, 0.12 mmol), and tosyl chloride (0.241 g, 1.27 mmol) were added successively. The mixture was stirred 3 h at room temperature, diluted with Et_2O (20 mL), and washed with 5% $NaHCO_3$ (10 mL), water (10 mL), and brine (10 mL). The organic phase was processed, and the residue was purified by column chromatography on silica gel (35% ethyl acetate/hexanes) to afford **17c** (0.46 g, 0.97 mmol), in 81% yield.

(2*S*,3*S*, 4*S*)-5-*O*-Benzyl-1-*O*-(*tert*-butyldimethylsilyl)-2,4-dimethyl-1,3,5-pentanetriol (18b). To a soln of **17a** (0.97 g, 2.4 mmol) in THF (5.0 mL) at 0 °C was added MeOH (0.1 mL), and a 0.5 M soln of $LiBH_4$ (2.4 mmol) in THF (4.7 mL) was added dropwise. After stirring 40 min at 0 °C a satd soln of sodium and potassium tartrate (15 mL) was added. The reaction mixture was allowed to warm to room temperature and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layer was washed with brine (20 mL) and processed.

The crude mixture was dissolved in CH_2Cl_2 (14 mL), and Et_3N (0.4 mL, 2.8 mmol), DMAP (0.030 g, 0.28 mmol), and TBDMSCl (0.42 g, 2.8 mmol) were added. After stirring 1 h at room temperature, the reaction mixture was diluted with Et_2O (20 mL), washed with satd NH_4Cl (20 mL) and brine (20 mL), and dried over $MgSO_4$. After filtration the solvent was removed under reduced pressure, and the crude product was chromatographed on flash silica gel to afford **18b** (0.675 g, 1.92 mmol, 80% yield, eluted with 5% ethyl acetate/hexanes) and (*R*)-4-benzyl-2-oxazolidinone (0.335 g, 1.89 mmol, 80% yield, eluted with 50% ethyl acetate/hexanes). **18b:** $[\alpha]^{25}_D = +18.6$ (*c* 1.6, $CHCl_3$); IR (film, NaCl): 3506, 2958, 2860, 1472, 1093 cm^{-1}; ^1H NMR (CCl_4): δ 0.07 (s, 6H), 0.82 (d, 3H, J = 6.9), 0.86 (d, 3H, J = 7.0), 0.90 (s, 9H), 1.6−1.7 (m, 1H), 1.8−1.9 (m, 1H), 3.0 (s, br, 1H), 3.4−3.6 (m, 5H), 4.53 (s, 2H), 7.20−7.30 (m, 5H); ^{13}C NMR: δ -5.7, −5.6, 8.8, 13.5, 18.0, 25.8, 35.6, 36.9, 67.1, 73.0, 74.9, 75.2, 127.2, 127.3, 128.1, 138.0. Anal. Calcd for $C_{20}H_{36}O_3Si$: C, 68.13, H, 10.29. Found: C, 68.37, H, 10.60.

(2*S*,3*S*,4*S*)-1-*O*-(*tert*-butyldimethylsilyl)-2,4-dimethyl-1,3,5-pentanetriol (18c). To a soln of **18b** (0.70 g, 2.0 mmol) in ethanol (10 mL) was added 10% Pd on charcoal (0.02 g), and the mixture was allowed to stir under hydrogen pressure (3 atm) for 7.5 h in a Parr apparatus. The reaction mixture was filtered over Celite, diluted with ether (30 mL), and washed with satd $NaHCO_3$ (3 × 15 mL) and brine (10 mL). The organic layer was processed, and purification by silica gel chromatography (20% ethyl acetate/hexanes) afforded **18c** (0.410 g, 1.56 mmol, 78% yield), as a colorless oil. $[\alpha]^{25}_D = +9.4$ (*c* 2.4, CH_2Cl_2); IR (film, NaCl): 3376, 2955, 2857, 1471, 1255, 1094 cm^{-1}; ^1H NMR: δ -0.11 (s, 6H), 0.56 (d, 3H, J = 6.9), 0.70 (s, 9H), 0.79 (d, 3H, J = 7.0), 1.50−1.60 (m, 1H), 1.60−1.70 (m, 1H), 3.40−3.50 (m, 2H), 3.53 (dd, 1H, J = 9.6 and 3.7), 3.59 (dd, 1H, J = 9.6 and 1.7), 3.67 (dd, 1H, J = 9.6 and 3.2). ^{13}C NMR (CCl_4): δ −5.8,−5.7, 8.9, 13.3, 17.9, 25.7, 36.3, 37.1, 68.0, 68.4, 79.3. Anal. Calcd for $C_{13}H_{30}SiO_3$: C, 59.49; H, 11.52. Found: C, 59.35; H, 11.78.

(2*S*,3*R*,4*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,4-dimethyl-1-*O*-*p*-toluenesulfonyl-1,3,5-pentanetriol (18e). (a) From 18c: To a soln of **18c** (0.27 g, 1.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C were added Et_3N (0.15 mL, 1.1 mmol), DMAP (0.012 g, 0.10 mmol), and *p*-toluenesulfonyl chloride (0.21 g, 1.1 mmol). After stirring 3 h at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and washed with water (5 mL), 1% aq HCl (5 mL), satd $NaHCO_3$ (5 mL), and brine (5 mL). The organic layer was normally processed, and the residue was purified by column chromatography on silica gel (10% ethyl acetate/hexanes) to afford **18e** (0.42 g, 1.0 mmol), in quantitative yield, as a colorless oil. $[\alpha]^{25}_D = -4.0$ (*c* 2.2, $CHCl_3$); IR (film, NaCl): 2928, 1359, 1177, 839 cm^{-1}; ^1H NMR (CCl_4): δ 0.08 (s, 6H), 0.88 (d, 3H, J = 7.0), 0.91 (d, 3H, J = 7.0), 0.92 (s, 9H), 1.65−1.75 (m, 1H), 1.75−1.85 (m, 1H), 2.48 (s, 3H), 2.75 (s, br, 1H), 3.57 (d, 1H, J = 9.6), 3.66 (dd, 1H, J = 8.3 and 4.7), 3.74 (dd, 1H, J = 8.3 and 3.7), 4.0−4.1 (m, 2H), 7.32 (d, 2H, J = 8.1), 7.77 (d, 2H, J = 8.1); ^{13}C NMR (CCl_4): δ −5.7, −5.6, 8.7, 13.3, 18.0, 21.4, 25.8, 35.5, 36.3, 68.3, 72.2, 73.5, 127.8, 129.2, 134.3, 143.1.

(b) From 17c: To a soln of **17c** (0.628 g, 1.32 mmol) in THF (10 mL) was added methanol (0.08 mL) followed by $LiBH_4$ (0.043 g, 2.0 mmol). The reaction mixture was stirred 1 h at 0 °C and quenched with 1.0 M sodium and potassium tartrate soln. After stirring 1 h at 0 °C, it was extracted with Et_2O (2 × 20 mL), and the organic extract was washed with brine (10 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (10 mL) followed by addition of Et_3N (0.21 mL, 0.15 g, 1.5 mmol), DMAP (0.018 g, 0.15 mmol), and TBDMSCl (0.23 g, 1.5 mmol). The reaction mixture was stirred 2 h at room temperature, diluted with Et_2O (40 mL), and washed with water (15 mL), 10% HCl (10 mL), and brine (10 mL). The organic phase was processed, and the residue was purified by column chromatography on silica gel, as described above, to afford **18e** (0.49 g, 1.2 mmol, 91% yield) and (*R*)-4-benzyl-2-oxazolidinone (0.20 g, 1.1 mmol, 83% yield).

(2*S*,3*R*,4*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,4-dimethyl-3-*O*-propionyl-1-*O*-*p*-toluenesulfonyl-1,3,5-pentanetriol (18f). To a soln of **18e** (0.40 g, 0.96 mmol) in CH_2Cl_2 (2.0 mL) were added Et_3N (0.15 mL, 0.11 g, 1.1 mmol), DMAP (0.012 g, 0.10 mmol), and propionic anhydride (0.20 mL, 0.20 g, 1.5 mmol). The reaction mixture was allowed to stir 30 min at room temperature, and it was diluted with CH_2Cl_2 (10 mL) and washed with 1% aq HCl (5 mL), satd $NaHCO_3$ (5 mL) and brine (5 mL), successively. The organic layer was dried over $MgSO_4$ and, filtered and the solvent removed under reduced pressure. Purification by column chromatography on silica gel (10% ethyl acetate/hexanes) afforded **18f** (0.43 g, 0.91 mmol), in 95% yield. $[\alpha]^{25}_D = -4.4$ (*c* 4.6 CH_2Cl_2); IR (film, NaCl): 2940, 1739, 1365, 1178 cm^{-1}; ^1H NMR (CCl_4): δ 0.00 (s, 6H), 0.82 (d, 3H, J = 6.9), 0.86 (s, 9H), 0.95 (d, 3H, J = 6.9), 1.09 (t, 3H, J = 7.6), 1.81−1.85 (m, 1H), 2.0−2.1 (m, 1H), 2.22 (q, 2H, J = 7.6), 2.45 (s, 3H), 3.31 (dd, 1H, J = 8.2 and 6.2), 3.38

(dd, 1H, J = 8.6 and 6.9), 3.74 (dd, 1H, J = 9.6 and 6.9), 3.92 (dd, 1H, J = 9.6 and 4.4), 4.87 (dd, 1H, J = 8.2 and 3.9), 7.30 (d, 2H, J = 8.3), 7.72 (d, 2H, J = 8.3); ^{13}C NMR (CCl_4): δ -5.8, −5.7, 9.0, 10.5, 14.0, 18.0, 21.3, 25.7, 26.9, 34.8, 36.9, 64.9, 70.7, 73.3, 127.9, 129.26, 134.1, 143.4, 172.2. Anal. Calcd for $C_{23}H_{40}SiO_6S$: C, 58.42; H, 8.53. Found: C, 58.55; H, 8.23.

(3*R*,5*S*,6*S*,1′*S*)-Tetrahydro-6-(1′-methyl-2′-(*tert*-butyldimethyl- silyloxy)ethyl)-3,5-dimethyl-2*H*-pyran-2-one (5a). To a soln of freshly sublimed *tert*-BuOK (0.095 g, 0.85 mmol) in THF (4.0 mL) at 0 °C was added dropwise a soln of **18f** (0.10 g, 0.21 mmol) in THF (1.0 mL). The reaction mixture was allowed to stir 30 min at room temperature and quenched with satd NH_4Cl (1.0 mL). The aqueous layer was extracted with Et_2O (3 × 5.0 mL), the combined organic layers were washed with brine (10 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (20% ethyl acetate/hexanes) to afford a 2:1 molar ratio of **5a**/**5b** (0.043 g, 0.14 mmol, 67% yield**)**, as determined by ^{1}H NMR (300 MHz). This mixture was dissolved in *tert*-BuOH (2.0 mL), *tert*-BuOK (0.017 g, 0.15 mmol) was added, and the reaction mixture was stirred 70 h at room temperature. The reaction was quenched with satd NH_4Cl (1.0 mL) and extracted with Et_2O (3 × 5 mL), and the combined organic phase was washed with brine (2 × 5 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by flash chromatography (10% ethyl acetate/hexanes) to afford **5a** (0.039 g, 0.13 mmol, 62% yield) as a colorless oil. $[\alpha]^{25}_D$ = +55.5 (*c* 2.7, $CHCl_3$); lit.[8]: $[\alpha]^{25}_D$ = +47.3 (*c* 2.7, $CHCl_3$); IR (film, NaCl): 1734, 1096, 837 cm^{-1}. ^{1}H NMR: δ 0.02 (s, 6H), 0.81 (d, 3H, J = 6.9), 0.85 (s, 9H), 0.92 (d, 3H, J = 6.4), 1.25 (d, 3H, J = 6.9), 1.34 (q, 1H, J = 13.1), 1.85−1.95 (m, 3H), 2.40−2.50 (m, 1H), 3.46 (dd, 1H, J = 9.8 and 6.1), 3.64 (dd, 1H, J = 9.7 and 8.7), 4.15 (d, 1H, J = 10.3). ^{13}C NMR: δ −5.4, 8.9, 17.1, 17.3, 18.2, 25.9, 30.6, 36.2, 37.4, 37.7, 64.6, 85.5, 174.6. Anal. Calcd for $C_{16}H_{32}O_3Si$: C, 63.95; H, 10.73. Found: C, 64.21; H, 10.95.

(4*S*)-*N*-[(2′*S*,3′*R*)-3′-Hydroxyl-2′-methyl-1′-oxopentyl]-4-benzyl-2-oxazolidinone (19). To a solution of oxazolidinone (−)-**16** (1.03 g, 4.42 mmol) in CH_2Cl_2 (9.0 mL) at 0 °C were added dropwise di-*n*-butylboron triflate (1.51 g, 5.52 mmol) and *N*,*N*-diisopropylethylamine (1.04 mL, 0.77 g, 5.98 mmol). After stirring 30 min at 0 °C, the reaction mixture was cooled to −78 °C, and propionaldehyde (0.64 mL, 0.51 g, 8.9 mmol) was added dropwise. The reaction mixture was stirred 45 min at −78 °C and 2 h at 0 °C, quenched with phosphate buffer (pH 7.0, 6 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The solvent was removed under reduced pressure, the residue was dissolved in methanol (10 mL), and a 3:1 (v/v) solution of methanol−20% H_2O_2 (15 mL) was added dropwise at 0 °C. After stirring 1 h at 0 °C, the reaction mixture was diluted with ether (40 mL), washed with 5% $NaHCO_3$ (30 mL), 10% HCl (30 mL), and brine (30 mL), and the organic phase was normally processed. The residue was purified by flash chromatography (15% ethyl acetate−hexanes) to afford (+)-**19** (0.98 g, 3.4 mmol), in 77% yield as a white solid (mp: 77−79 °C). $[\alpha]^{25}_D$ = +38.5 (*c* 1.07, $CHCl_3$); IR (KBr): 3524, 2975, 1761, 1700, 1388, 1221 cm^{-1}; ^{1}H NMR: δ 0.98 (t, 3H, J = 7.4), 1.25 (d, 3H, J = 7.1), 1.4−1.7 (m, 2H), 2.80 (dd, 1H, J = 13.3 and 9.3), 2.95 (s, br, 1H), 3,25 (dd, 1H, J = 13.3 and 3.4), 3.80 (dq, 1H, J = 7.1 and 2.7), 3.8−3.9 (m, 1H), 4.1−4.3 (m, 2H), 4.7−4.8 (m, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR: δ 10.3, 10.5, 26.8, 37.9, 41.8, 55.2, 63.3, 73.1, 127.7, 129.2, 129.7, 135.3, 153.3, 177.8.

(2*S*,3*R*)-*N*-Methyl-N-methoxy-3-hydroxy-2-methylpentanamide (20). To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (1.18 g, 12.1 mmol) in CH_2Cl_2 was added dropwise a 2.0 M solution of trimethylaluminum in toluene (6.13 mL, 12.3 mmol). After stirring 1 h at room temperature, the mixture was cooled to −20 °C, and a solution of (−)-**19** (1.73 g, 5.94 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was let to warm to room temperature and stirred 1.5 h. The reaction was quenched with 1.0 M tartaric acid (30 mL), and after stirring 15 h at room temperature, the organic layer was separated and the aqueous one was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was processed, and the residue was purified by flash chromatography (30% ethyl acetate−hexanes) to afford amide (+)-**20** (0.96 g, 5.5 mmol), in 93% yield and (S)-4-benzyl-2-oxazolidinone (0.89 g, 5.0 mmol, 84% yield). Amide (+)-**20**: $[\alpha]_D$ = +17.0 (*c* 2.0, CH Cl_3); IR (film, NaCl): 3407(br), 2972, 1637, 1460, 1390, 979 cm^{-1}; ^{1}H-NMR: δ 0.94 (t, 3H, J = 7.4), 1.14 (d, 3H, J = 7.1), 1.35−1.50 (m, 1H), 1.50−1.65 (m, 1H), 2.00 (s, br, 1H), 2.90 (s, br, 1H), 3.18 (s, 3H), 3.69 (s, 3H), 3.70−3.80 (m, 1H). ^{13}C NMR: δ 10.0, 10.3, 26.7, 31.8, 38.1, 61.5, 73.0, 173.1.

(2*S*,3*R*)-*N*-Methyl-*N*-methoxy-2-methyl-3-(*tert*-butyldimethylsilyloxy) pentanamide (21). To a solution of amide **20** (0.200 g, 1.14 mmol) in DMF (0.4 mL) were added imidazole (0.194 g, 2.85 mmol) and TBSCl (0.206 g, 1.37 mmol). The reaction mixture was stirred 24 h at room temperature, diluted with hexanes (10 mL), and washed with water (5 mL) and brine (5 mL). The organic phase was processed, and the crude product was purified by flash chromatography (15% ethyl acetate−hexanes) to afford amide **21** (0.250 g, 0.865 mmol), in 76% yield. $[\alpha]_D$ = + 3.9 (*c* 2.2, CH_2Cl_2); IR (film, NaCl): 2959, 2935, 2884, 2857, 1665, 1463, 1383, 1254, 1048, 1000 cm^{-1}; ^{1}H NMR: δ 0.06 (s, 6H), 0.87 (t, 3H, J = 7.5), 0.90 (s, 9H), 1.15 (d, 3H, J = 6.9), 1.40−1.60 (m, 2H), 3.00 (s, br, 1H), 3.17 (s, 3H), 3.69 (s, 3H), 3.89 (dt, 1H, J = 8.0 and 4.7); ^{13}C NMR: δ -4.4, −4.2, 8.5, 14.7, 18.2, 26.0, 28.2, 32.2., 40.1, 61.4, 74.2, 176.7.

(2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-2-methylpentanal (22). To a solution of amide **21** (0.24 g, 0.83 mmol) in toluene (2.0 mL) at −78 °C was added DIBAL-H in toluene (1.66 mL of a 1.0 M soln in toluene, 1.66 mmol), and the reaction mixture was stirred 1.5 h at −78 °C. The reaction was quenched with ethyl acetate (1.0 mL), poured into a mixture containing CH_2Cl_2 (4.0 mL) and 1 M HCl (10.0 mL) and stirred 30 min at room temperature. The organic layer was separated, and the aqueous one was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with satd aq NH_4Cl (20 mL) and a satd aq soln of sodium and potassium tartrate (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography (5% ethyl acetate−hexanes) to yield aldehyde **22** (0.15 g, 0.65 mmol), in 78% yield. $[\alpha]_D$ = + 67.2 (*c* 3.1, CH_2Cl_2); IR (film, NaCl): 2958, 2932, 2882, 1727, 1463, 1254, 1048, 837, 775 cm^{-1}; ^{1}H NMR (CCl_4): δ 0.04 (s, 3H), 0.07 (s, 3H), 0.87 (s, 9H), 0.89 (t, 3H, J = 7.2), 1.06 (d, 3H, J = 6.9), 1.44−1.62 (m, 2H), 2.42−2.52 (m, 1H), 4.02 (dt, 1H, J = 7.2 and 3.6), 9.77 (d, 1H, J = 1.0); ^{13}C NMR (CCl_4): δ −4.7, −4.2, 7.5, 10.1, 18.0, 25.7, 27.4, 50.8, 73.4, 205.5.

(*E*)-(3*R*,4*R*)-1-Iodo-3-methyl-4-(*tert*-butyldimethylsilyloxy)-1-hexene (23). To a suspension of $CrCl_2$ (0.218 g, 1.77 mmol) in degassed THF (8.5 mL) at 0 °C were added iodoform (0.167 g, 0.424 mmol) and a solution of aldehyde **22** (0.050 g, 0.22 mmol) in THF (2.0 mL). The reaction mixture was stirred 1.5 h at 0 °C, and the reaction was quenched with water (5 mL). The organic layer was separated, and the aqueous one was saturated with NaCl and extracted with ether (3 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexanes) to yield vinylic iodide **23** (0.045 g, 0.13 mmol), in 59% yield. $[\alpha]_D$ = +32.2 (*c* 3.9, CH_2Cl_2); IR (film, NaCl): 2958, 2928, 2855, 1602, 1462, 1016, 834 cm^{-1}; ^{1}H NMR (CCl_4): δ 0.00 (s, 6H), 0.81 (t, 3H, J = 7.5), 0.85 (s, 9H), 0.93 (d, 3H, J = 6.9), 1.35−1.45 (m, 2H), 2.22−2.32 (m, 1H), 3.42 (q, 1H, J = 4.3), 5.93 (dd, 1H, J = 14.5 and 1.0), 6.42 (dd, 1H, J = 14.5 and 7.8); ^{13}C NMR (CCl_4, 75.5 MHz): δ −4.5, −4.3, 9.5, 13.7, 18.0, 25.8, 26.6, 44.7, 74.4, 76.1, 149.0.

(*E*)-(3*R*,4*R*)-6-Iodo-4-methyl-5-hexen-3-ol (6b). A 0.85 mL volume of a soln of HF prepared from 48% aq HF (0.5 mL), CH_3CN (8.5 mL), and water (0.5 mL) was added to vinylic iodide **23** (0.150 g, 0.424 mmol), and the mixture was stirred 4 h at room temperature. After dilution of the reaction mixture with ether (15 mL) and neutralization with satd $NaHCO_3$, the organic phase was washed with water (2 × 3.0

mL) and brine (3.0 mL). The organic layer was normally processed, and the crude product was purified by column chromatography (50% ethyl acetate in hexanes) to yield **6b** (0.096 g, 0.400 mmol), in 94% yield). $[\alpha]_D = +28.0$ (*c* 2.9, CH_2Cl_2); IR (film, NaCl): 3400 (br), 3080, 2982, 2955, 2880, 1600, 1464, 946 cm^{-1}; ^1H NMR: δ 0.94 (t, 3H, $J = 7.4$), 1.03 (d, 3H, $J = 6.8$), 1.29−1.44 (m, 1H), 1.47−1.64 (m, 2H), 2.26−2.37 (m, 1H), 3.40 (dt, 1H, $J = 5.1$ and 8.8), 6.09 (dd, 1H, $J = 14.4$ and 1.0), 6.52 (dd, 1H, $J = 14.4$ and 8.1); ^{13}C NMR: δ 10.2, 13,9, 26.9, 46.1, 75.4, 75.7, 148.7.

(2*S*,3*S*,4*S*,6*R*)-2,4,6-Trimethyl-1,3,7-heptanetriol. To a suspension of $LiAlH_4$ (0.050 g, 1.3 mmol) in THF (2.0 mL) at 0 °C was added dropwise a solution of **5a** (0.204 g, 0.68 mmol) in THF (1.0 mL). The reaction mixture was let to warm to room temperature and to stir for 22 h. The reaction was quenched at 0 °C by the addition of water (0.050 mL), 15% aq KOH (0.050 mL), and water (0.150 mL), successively, and kept 24 h under vigorous stirring at room temperature. The inorganic solids were filtered off and washed with ether (3 × 10 mL), and the solvent was removed under reduced pressure. The crude product was eluted through a pad of silica gel with ethyl acetate to yield (2*S*,3*S*,4*S*,6*R*)-2,4,6-trimethyl-1,3,7-heptanetriol (0.122 g, 0.642 mmol), in 94% yield. $[\alpha]_D = -8.9$ (*c* 1.9, $CHCl_3$); IR (film, NaCl): 3350 (br), 2982, 2950, 2900, 1473, 1400, 1054, 1000 cm^{-1}; ^1H NMR: δ 0.83 (d, 3H, $J = 6.6$), 0.88 (d, 3H, $J = 6.9$), 0.80−0.90 (m, 1H), 0.95 (d, 3H, $J = 6.6$), 1.6−1.9 (m, 4H), 3.37−3.46 (m, 2H), 3.57−3.65 (m, 3H), 3.9−4.3 (m, br, 3H); ^{13}C NMR: δ 8.9, 16.7, 18.8, 33.2, 34.1, 36.1, 37.3, 66.1, 67.1, 78.2; HRMS calcd for $C_{10}H_{22}O_3$: 190.1569. Found: 190.1571.

(2*R*,4*S*)-4-[(2′*R*,4′*S*,5′*S*)-2′-(4-Methoxyphenyl)-5′-methyl-1′,3′-dioxan-4-yl]-2-methylpentan-1-ol (24). A solution of the aforementioned triol (0.112 g, 0.589 mmol), *p*-anisaldehyde dimethylacetal (0.128 g, 0.703 mmol), and camphorsulfonic acid (0.0068 g, 0.030 mmol) in CH_2Cl_2 (3.0 mL) was stirred 12 h at room temperature and quenched with satd $NaHCO_3$ (1.0 mL). The mixture was diluted with ether (10 mL), and the organic layer was washed with water (2.0 mL) and brine (2.0 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (30% ethyl acetate−hexanes) to afford alcohol **24** (0.178 g, 0.578 mmol), in 98% yield. $[\alpha]_D = -39.7$ (*c* 1.5, $CHCl_3$). IR (film, NaCl): 3445 (br), 2982, 2945, 2890, 2864, 1605, 1400, 1264 cm^{-1}; ^1H NMR: δ 0.86 (d, 3H, $J = 6.8$), 0.85−0.95 (m, 1H), 0.93 (d, 3H, $J = 6.4$), 1.15 (d, 3H, $J = 6.9$), 1.6−1.8 (m, 5H), 3.40−3.50 (m, 3H), 3.79 (s, 3H), 4.02 (d, 2H, $J = 1.8$), 5.42 (s, 1H), 6.87−6.90 (m, 2H), 7.38−7.41 (m, 2H); ^{13}C NMR: δ 10.8, 15.6, 18.6, 31.1., 32.4, 33.6, 37.4, 55.2, 67.1, 73.9, 85.0, 101.9, 113.6, 127.2, 131.3, 159.8; HRMS calcd for $C_{18}H_{28}O_4$: 308.1988. Found: 308.1987.

(2*R*,4*S*)-4-[(2′*R*,4′*S*,5′*S*)-2′-(4-Methoxyphenyl)-5′-methyl-1′,3′-dioxan-4-yl]-2-methyl-1-(triisopropylsilyloxy)pentane (25). A solution of alcohol **24** (0.120 g, 0.390 mmol), imidazole (0.120 g, 1.76 mmol), and triisopropylsilyl chloride (0.150, 0.779 mmol) in DMF (0.5 mL) was stirred 24 h at room temperature, diluted with ether (20 mL), and washed with water (2 × 1 mL) and brine (1 mL). The organic layer was processed, and the crude product was purified by column chromatography (20% ethyl acetate−hexanes) to yield **25** (0.181 g, 0.390 mmol), in quantitative yield. $[\alpha]_D = -27.7$ (*c* 1.8, $CHCl_3$); IR (film, NaCl): 2964, 2950, 2864, 1618, 1520, 1464, 1263, 1120 cm^{-1}; ^1H NMR: δ 0.84 (d, 3H, $J = 6.7$), 0.82−0.88 (m, 1H), 0.93 (d, 3H, $J = 6.4$), 1.02 (s, 3H), 1.03 (s, 18H), 1.14 (d, 3H, $J = 6.8$), 1.60−1.90 (m, 4H), 3.36−3.43 (m, 2H), 3.56 (dd, 1H, $J = 4.6$ and 4.5), 3.8 (s, 3H), 3.97−4.07 (m, 2H), 5.41 (s, 1H), 6.85−6.88 (m, 2H), 7.39−7.43 (m, 2H); ^{13}C NMR: δ 10.9, 11.9, 14.9, 18.0, 18.7, 30.1, 32.3, 33.5, 37.7, 55.2, 68.2, 74.0, 84.9, 101.5, 113.3, 127.2, 131.7, 159.6; HRMS calcd for $C_{27}H_{48}O_4Si$: 464.3322. Found: 464.3237.

(2*S*,3*S*,4*S*,6*R*)-3-(4-Methoxybenzyloxy)-7-(triisopropylsilyloxy)-2,4,6-trimethylheptan-1-ol (26). To a solution of **25** (0.149 g, 0.321 mmol) in toluene (2.0 mL) at 0 °C was added dropwise a 1 M solution of DIBAL-H in toluene (0.96 mL, 0.96 mmol). The reaction mixture was stirred 1 h at 0 °C and quenched with ethyl acetate (1.0 mL), followed by the addition of satd soln of sodium and potassium tartrate (1.0 mL). The mixture was vigorously stirred for 6 h and extracted with ether (4 × 10 mL). The organic layer was washed with brine (3.0 mL) and processed. The crude product was purified by column chromatography (25% ethyl acetate−hexanes) to afford **26** (0.148 g, 0.317 mmol), in 99% yield. $[\alpha]_D = +7.8$ (*c* 2.1, $CHCl_3$); IR (film, NaCl): 3400 (br), 2965, 2880, 1620, 1520, 1472, 1260 cm^{-1}; ^1H NMR: δ 0.85−1.10 (m, 1H), 0.94 (d, 6H, $J = 6.8$), 0.95 (d, 3H, $J = 6.7$), 1.04−1.06 (m, 21H), 1.60−2.00 (m, 5H), 3.33 (dd, 1H, $J = 3.0$ and 6.4), 3.44−3.48 (m, 1H), 3.54−3.59 (m, 3H), 3.80 (s, 3H), 4.50 (AB system, 2H, $J = 11.0$, $\Delta\nu_{AB} = 40.6$), 6.86 (d, 2H, $J = 8.6$), 7.26 (d, 2H, $J = 8.6$); ^{13}C NMR: δ 11.5, 11.9, 16.8, 18.0, 18.5, 32.9, 33.5, 37.0, 37.2, 55.2, 67.0, 68.1, 73.2, 84.1, 113.7, 129.1, 131.1, 159.0; HRMS calcd for $C_{27}H_{50}O_4Si$: 466.3478. Found: 466.3435.

(2*R*,3*S*,4*S*,6*R*)-3-(4-Methoxybenzyloxy)-7-(triisopropylsilyloxy)-2,4,6-trimethylheptanoic Acid (27). To a solution of alcohol **26** (0.019 g, 0.041 mmol) in acetone (1.0 mL) at 0 °C was added Jones reagent (0.060 mL, 0.085 mmol). After 20 min stirring at 0 °C, an additional amount of Jones reagent was added (0.030 mL, 0.042 mmol). After 40 min stirring at 0 °C, the reaction was quenched with 2-propanol (0.15 mL, let to warm to room temperature, and diluted with ether (10 mL). The organic layer was normally processed, and the crude product was purified by filtration through a pad of silica gel (50% ethyl acetate−hexanes) to afford **27** (0.014 g, 0.029 mmol), in 71% yield. $[\alpha]_D = -5.3$ (*c* 1.6, $CHCl_3$); IR (film, NaCl) 3600−2400, 2962, 2873, 1710, 1512, 1480, 1250 cm^{-1}; ^1H NMR: δ 0.90−1.10 (m, 1H), 0.93 (d, 3H, $J = 6.7$), 0.95 (d, 3H, $J = 7.1$), 1.03−1.05 (m, 21H), 1.21 (d, 3H, $J = 7.0$), 1.55−1.90 (m, 3H), 2.74 (dq, 1H, $J = 6.9$ and 5.4), 3.37 (dd, 1H, $J = 9.5$ and 4.7), 3.57 (dd, 1H, $J = 9.6$ and 4.7), 3.61 (t, 1H, $J = 5.7$), 3.78 (s, 3H), 4.48 (s, 2H), 6.85 (d, 2H, $J = 8.7$), 7.23 (d, 2H, $J = 8.7$); ^{13}C NMR: δ 11.3, 11.8, 16.9, 17.9, 18.5, 33.5, 34.2, 36.6, 41.5, 55.1, 68.0, 73.8, 84.2, 113.7, 129.3, 130.8, 159.2, 182.2; HRMS calcd for $C_{27}H_{48}O_5Si$: 480.3271. Found: 480.3297.

(*E*)-(2*R*,3*S*,4*S*,6*R*,3′*R*,4′*R*)-6′-Iodo-3′-methyl-1′-hexen-4′-yl 3-(4-Methoxybenzyloxy)-7-(triisopropylsilyloxy)-2,4,6-trimethylheptanoate (28). To a solution of carboxylic acid **27** (0.050 g, 0.10 mmol) in THF (1.0 mL) at room temperature were added triethylamine (0.019 mL, 0.014 g, 0.135 mmol) and 2,4,6-trichlorobenzoyl chloride (0.0305 g, 0.125 mmol). The reaction mixture was stirred 2 h at room temperature, and the solids were filtered off and washed with hexanes. The solvent was evaporated under reduced pressure, the residue was dissolved in benzene (1.5 mL), and a solution of alcohol **6b** (37.5 mg, 0.156 mmol) and DMAP (0.0165 g, 0.135 mmol) in benzene (0.5 mL) was added. After stirring 24 h at room temperature, the reaction was diluted with ether (20 mL), washed with satd $NaHCO_3$ (2.0 mL) and brine (2.0 mL), and dried over $MgSO_4$. The organic phase was processed, and the crude product was purified by column chromatography (20% ethyl acetate−hexanes) to yield **28** (0.068 g, 0.097 mmol), in 97% yield. $[\alpha]_D = +56.7$ (*c* 1.2, $CHCl_3$); IR (film, NaCl): 2980, 2955, 2872, 1735, 1510, 1475, 1250 cm^{-1}; ^1H NMR: δ 0.86 (t, 3H, $J = 7.3$), 0.94 (d, 3H, $J = 6.9$), 0.94−1.15 (m, 1H), 0.97 (d, 3H, $J = 7.5$), 1.02 (d, 3H, $J = 6.8$), 1.04−1.06 (m, 21H), 1.23 (d, 3H, $J = 7.1$), 1.48−1.86 (m, 5H), 2.42−2.54 (m, 1H), 2.70 (dq, 1H, $J = 7.0$ and 1.5), 3.35 (dd, 1H, $J = 9.5$ and 7.0), 3.54−3.62 (m, 2H), 3.80 (s, 3H), 4.48 (s, 2H), 4.74 (dt, 1H, $J = 8.0$ and 5.1), 6.07 (dd, 1H, $J = 14.5$ and 1.0), 6.47 (dd, 1H, $J = 14.5$ and 7.8), 6.85 (m, 2H), 7.25 (m, 2H); ^{13}C NMR: δ 9.4, 11.6, 12.4, 14.4, 16.9, 18.8, 18.3, 23.6, 33.5, 34.3, 36.1, 42.1, 43.1, 55.1, 68.0, 73.6, 75.9, 77.1, 84.0, 113.7, 129.2, 131.1, 147.6, 158.2, 175.8; HRMS calcd for $C_{34}H_{59}O_5SiI$: 702.3176. Found: 702.3174.

(*E*)-(2*R*,3*S*,4*S*,6*R*,3′*R*,4′*R*)-6′-iodo-3′-methyl-1′-hexen-4′-yl 3-(4-Methoxybenzyloxy)-7-hydroxy-2,4,6-trimethylheptanoate. Ester **28** (0.036 g, 0.051 mmol) was treated at room temperature with 0.030 mL of a solution containing 48% HF (0.5 mL), acetonitrile (8.6 mL), and water (0.9 mL), added every 3 h. After addition of five aliquots every 3 h, the reaction mixture was stirred 5 h at room temperature, diluted with ether (5 mL), and neutralized with satd $NaHCO_3$ (1 mL). The organic layer was separated, the aqueous layer was extracted

with ether (2 × 3.0 mL), and the combined organic extract was washed with water (1.0 mL) and brine (1.0 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (30% ethyl acetate−hexanes) to afford the desired alcohol (0.026 g, 0.048 mmol), in 94% yield. $[\alpha]_D = +46.0$ (*c* 1.0, $CHCl_3$); IR (film, NaCl): 3327, 2935, 2865, 1715, 1640, 1530, 1464, 1390 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, 3H, *J* = 7.3), 0.95 (d, 3H, *J* = 6.5), 0.98 (d, 3H, *J* = 6.7), 0.90−1.03 (m, 1H), 1.03 (d, 3H, *J* = 6.9), 1.25 (d, 3H, *J* = 7.0), 1.50−1.90 (m, 6H), 2.50 (dt, 1H, *J* = 1.0 and 6.0), 2.75 (qt, 1H, *J* = 6.7), 3.42 (d, 2H, *J* = 4.8), 3.55 (dd, 1H, *J* = 6.5 and 4.7), 3.80 (s, 3H), 4.49 and 4.54 (AB system, 2H, *J* = 10.7, $\Delta\nu$ = 14.5 Hz), 4.75 (dt, 1H, *J* = 8.6 and 5.1), 6.08 (dd, 1H, *J* = 14.5 and 1.0), 6.47 (dd, 1H, *J* = 14.5 and 7.8), 6.86−6.89 (m, 2H), 7.25−7.28 (m, 2H). ^{13}C NMR ($CDCl_3$, 75.5 MHz): δ 10.2, 13.5, 15.0, 18.2, 18.8, 24.2, 33.5, 34.7, 35.6, 43.2, 43.6, 55.6, 67.2, 74.8, 76.5, 77.8, 84.9, 114.1, 129.7, 131.0, 147.6, 159.5, 175.9. HRMS calcd for $C_{25}H_{39}O_5$: 546.1842. Found: 546.1844.

(2*R*,3*S*,4*S*,6*R*,3′*R*,4′*R*)-(*E*)-6′-iodo-3′-methyl-1′-hexen-4′-yl 3-(4-Methoxybenzyloxy)-6-formyl-2,4-dimethylheptanoate (29). To a suspension of Dess−Martin periodinane (0.022 g, 0.051 mmol) in CH_2Cl_2 (0.1 mL) was added a solution of the alcohol prepared above (0.011 g, 0.020 mmol) and pyridine (0.017 g, 0.21 mmol) in CH_2Cl_2. The reaction mixture was stirred 8 h at room temperature, and it was diluted with ethyl acetate (3.0 mL). After the addition of satd $NaHCO_3$ (0.5 mL), the organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 2.0 mL). The combined organic layers were washed with 1.0 M $Na_2S_2O_3$ (1.0 mL) and dried under $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was filtered through a pad of silicagel (70% ethyl acetate-benzene) to yield aldehyde **29** (0.011 g, 0.020 mmol), in quantitative yield. ^1H NMR: δ 0.87 (t, 3H, *J* = 7.3), 0.98 (d, 3H, *J* = 6.9), 1.03 (d, 3H, *J* = 6.6), 1.09 (d, 3H, *J* = 6.9), 1.0−1.2 (m, 1H), 1.25 (d, 3H, *J* = 6.9), 1.45−1.75 (m, 3H), 1.97 (ddd, 1H, *J* = 14.0, 9.6, 4.3), 2.40−2.60 (m, 2H), 2.73 (qt, 1H, *J* = 6.9), 3.59 (dd, 1H, *J* = 5.7 and 5.1), 3.80 (s, 3H), 4.51 (AB system, 2H, *J* = 10.8, $\Delta\nu$ = 20.5 Hz), 4.75 (dt, 1H, *J* = 8.0 and 5.1), 6.09 (dd, 1H, *J* = 14.6 and 1.1), 6.48 (dd, 1H, *J* = 14.6 and 7.7), 6.85−6.92 (m, 2H), 7.24−7.28 (m, 2H), 9.5 (d, 1H, *J* = 2.9). ^{13}C NMR: δ 9.5, 12.7, 14.3, 14.5, 17.0, 23.6, 33.0, 34.4, 42.6, 43.0, 44.0, 55.1, 74.3, 76.0, 77.4, 84.1, 113.8, 129.4, 130.8, 147.6, 150.4, 175.5, 205.8.

(2*R*,3*S*,4*S*,6*R*,7*R*/*S*,10*R*,11*R*)-(*E*)-11-Ethyl-7-hydroxy-3-(4-methoxybenzyloxy)- 2,4,6,10-tetramethyl-8-dodecenolide (30a and 30b). To a suspension of $CrCl_2$ (0.035 g, 0.29 mmol) containing 1% mol of $NiCl_2$ (0.0075 g, 0.0058 mmol) in degassed DMF (3.5 mL) was added, under ice bath, a solution of **29** (0.015 g, 0.027 mmol) in DMF (1.5 mL). The reaction mixture was stirred 12 h at room temperature, and the solvent was removed under vacuum (0.1 mmHg). The residue was dissolved in water (1.0 mL) and extracted with ether (4 × 5 mL). The organic layer was washed with water (2 × 2.0 mL) and brine (2.0 mL) and processed. The crude product was purified by flash chromatography (20% ethyl acetate−hexanes) to yield a 1:1 mixture of **30a** and **30b** (0.0085 g, 0.020 mmol) in 74% yield. More polar isomer (**30a**): IR (film, NaCl): 3500 (br), 2990, 1735, 1610 cm^{-1}; ^1H NMR: δ 0.89−1.05 (m,1H), 0.91 (t, 3H, *J* = 7.4), 0.96 (d, 3H, *J* = 7.0), 1.05 (d, 3H, *J* = 6.9), 1.11 (d, 3H, *J* = 6.8), 1.27 (d, 3H, *J* = 6.9), 1.5−1.7 (m, 4H), 1.86−2.0 (m, 2H), 2.54−2.62 (s,br, 1H), 2.68 (dq, 1H, *J* = 6.7 and 3.5), 3.45 (dd, 1H, *J* = 10.0 and 1.5), 3.8 (s, 3H), 4.11 (s, br, 1H), 4.57 (AB system, 2H, *J* = 10.6, $\Delta\nu$ = 15.8 Hz), 5.0 (ddd, 1H, *J* = 8.8, 5.4 and 3.2), 5.55 (ddd, 1H, *J* = 15.8, 3.5 and 1.6), 5.69 (ddd, 1H, *J* = 15.8, 4.4, 1.6), 6.87 (d, 2H, *J* = 7.5), 7.2 (d, 2H, *J* = 7.5); ^{13}C NMR: δ 10.4, 10.7, 16.4, 17.7, 20.4, 24.4, 32.9, 33.5, 35.4, 37.7, 43.4, 55.2, 75.8, 76.2, 77.2, 86.6, 113.7, 128.5, 129.2, 130.7, 130.9, 159.1, 175.7. Less polar isomer (**30b**): IR (film, NaCl): 3500 (br), 1732, 1615 cm^{-1}; ^1H NMR: δ 0.90−1.14 (m, 1H), 0.90 (t, 3H, *J* = 7.4), 0.96 (d, 3H, *J* = 6.7), 1.05 (d, 3H, *J* = 6.6), 1.07 (d, 3H, *J* = 6.7), 1.27 (d, 3H, *J* = 6.8), 1.5−1.7 (m, 4H), 1.95−2.05 (m, 2H), 2.44−2.54 (s, br, 1H), 2.64 (dq, 1H, *J* = 6.8 and 3.5), 3.46 (dd, 1H, *J* = 10.3 and 1.5), 3.80 (s, 3H), 4.15 (dd, 1H, *J* = 10.0 and 5.0), 4.57 (AB system, 2H, *J* = 10.6, $\Delta\nu$ = 13.0), 5.04 (ddd, 1H, *J* = 8.6, 5.5 and 2.9), 5.52 (ddd, 1H, *J* = 15.5, 9.7 and 1.9), 5.70 (dd, 1H, *J* = 15.5 and 3.1), 6.86 (m, 2H), 7.26 (m, 2H); ^{13}C NMR: δ 9.5, 10.3, 14.5, 16.3, 17.5, 24.8, 31.6, 33.0, 33.2, 37.9, 43.5, 55.2, 74.0, 75.5, 76.4, 86.8, 113.7, 126.6, 129.2, 130.8, 137.8, 159.2, 175.8; HRMS calcd for $C_{25}H_{38}O_5$: 418.2719. Found: 418.2715.

(2*R*,3*S*,4*S*,6*R*,10*R*,11*R*)-(*E*)-11-Ethyl-7-oxo-3-(4-methoxybenzyloxy)-2,4,6,10-tetramethyl-8-dodecenolide (31). To a suspension of Dess−Martin periodinane (0.101 g, 0.248 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added a soln in CH_2Cl_2 (0.5 mL) of pyridine (0.0078 g, 0.99 mmol) and allylic alcohols **30a/30b** (0.013 g, 0.031 mmol). The reaction mixture was stirred 12 h at room temperature and quenched with ethyl acetate (2.0 mL) and filtered. The organic layer was washed with satd $NaHCO_3$ (1.0 mL) and processed. The crude product was purified by flash chromatography (20% ethyl acetate−hexanes) to afford the **31** (0.010 g, 0.024 mmol) in 77% yield. $[\alpha]_D = +97.2$ (*c* 1.0, $CHCl_3$); IR (film, NaCl): 2964, 2935, 1735, 1700, 1630, 1180 cm^{-1}; ^1H NMR: δ 0.91 (t, 3H, *J* = 7.4), 1.05−1.80 (m, 5H), 1.06 (d, 3H, *J* = 6.6), 1.10 (d, 3H, *J* = 6.8), 1.19 (d, 3H, *J* = 7.0), 1.30 (d, 3H, *J* = 6.9), 2.48−2.79 (m, 3H), 3.45 (d, 1H, *J* = 10.2), 3.80 (s, 3H), 4.57 (AB system, 2H, *J* = 10.4, $\Delta\nu$ = 13.0), 4.97 (ddd, 1H, *J* = 8.4, 5.7, 2.5), 6.41 (dd, 1H, *J* = 15.7 and 1.2), 6.74 (dd, 1H, *J* = 15.7 and 5.4), 6.80 (d, 2H, *J* = 8.7), 7.26 (d, 2H, *J* = 8.7); ^{13}C NMR: δ 9.5, 10.3, 16.3, 17.6, 18.2, 25.1, 34.0, 34.1, 37.9, 43.5, 45.1, 55.2, 73.6, 76.4, 86.3, 113.8, 125.8, 129.2, 130.6, 146.8, 159.2, 175.0, 205.1; HRMS calcd for $C_{25}H_{36}O_5$: 416.2563. Found: 416.2550.

(2*R*,3*S*,4*S*,6*R*,10*R*,11*R*)-(*E*)-11-Ethyl-7-oxo-3-hydroxy-2,4,6,10-tetramethyl-8-dodecenolide (2c). To a solution of the macrolide above (0.010 g, 0.025 mmol) in CH_2Cl_2 (1.2 mL) were added water (0.063 mL, 0.063 g, 3.5 mmol) and DDQ (0.011 g, 0.050 mmol). The reaction mixture was stirred 1.5 h at room temperature and diluted with CH_2Cl_2 (2.0 mL) and satd $NaHCO_3$ (0.1 mL). The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (2 × 1.0 mL). The combined organic phase was processed, and the crude product was purified by flash chromatography (30% ethyl acetate−hexanes) to yield **2c** (0.007 g, 0.024 mmol), in 96% yield. $[\alpha]_D = +89.0$ (*c* 0.86, $CHCl_3$); IR (film, NaCl): 3464 (br), 2974, 2927, 2860, 1727, 1702, 1620 cm^{-1}; ^1H NMR: δ 0.91 (t, 3H, *J* = 7.3), 1.0 (d, 3H, *J* = 6.2), 1.12 (d, 3H, *J* = 6.6), 1.22 (d, 3H, *J* = 6.9), 1.30 (d, 3H, *J* = 6.6), 1.20−1.37 (m, 2H), 1.47−1.78 (m, 4H), 2.46−2.66 (m, 3H), 3.56 (d, 1H, *J* = 10.4), 5.00 (ddd, 1H, *J* = 8.5, 5.7 and 2.2), 6.42 (dd, 1H, *J* = 15.7 and 1.2), 6.78 (dd, 1H, *J* = 15.7 and 5.4); ^{13}C NMR: δ 9.3, 10.0, 16.1, 17.2, 17.4, 24.9, 33.0, 33.2, 37.8, 43.2,, 45.0, 73.7, 78.2, 125.8, 147.3, 175.1, 205.4; HRMS calcd for $C_{17}H_{28}O_4$: 296.1988. Found: 296.1987.

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Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **5a**, **6**, **17c**, **25**, **27**, **28**, **30a**, **30b**, 10-deoxymethynolide (**2c**) and its 3-*O*-*p*-methoxybenzyl derivative (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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