N^{ϵ}-Cinnamoyl-N^{ϵ}-hydroxy-L-lysine Methyl Ester, Trifluoroacetic Acid Salt (6). Trifluoroacetic acid (TFA) (5.0 mL) was added dropwise over 30 s to N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-N^{α}-BOC-L-lysine methyl ester (5) (0.340 g, 0.8365 mmol) at 0 °C under nitrogen. The ice bath was removed and the solution stirred for 5 min. TLC (7% EtOH/$CHCl_3$) showed the reaction was complete after this time. The volatiles were removed under high vacuum to give the desired N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester, trifluoroacetic acid salt (0.351 g, 100%): ^{1}H NMR ($CDCl_3$) (90 MHz) δ 7.30 (broad m, 7 H, aromatic), 4.02 (broad m, 1 H, CH), 3.72 (m, 2 H, CH_2), 3.70 (s, 3 H, OCH_3), 1.90 (m, 2 H, CH_2), 1.62 (m, 4 H, CH_2); mass spectrum (positive FAB) M^+ = 307, $C_{16}H_{23}N_2O_4$ (307.37) expected for cation.

N^{α},$N^{\alpha'}$-[Hydroxy-3-(*tert*-butoxycarbonyl)glutaryl]bis-[N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester] (7). Compound 7 was synthesized by two methods. In method 1, a 10% (by volume) NH_3/MeOH solution (0.1 mL) was added dropwise to 4 (10.1 mg, 0.0098 mmol). The reaction was carried out under nitrogen at -23 °C. The reaction was monitored by TLC (5% EtOH/$CHCl_3$). After 30 min, the solvents were removed under high vacuum, and the resulting oil was purified by column chromatography (4 g of SiO_2 eluted with 5% EtOH/$CHCl_3$) to give pure nannochelin A *tert*-butyl ester, 7 (2.3 mg, 29%).

In method 2, intermediate 6 was reacted immediately with 2-*tert*-butyl 1,3-di-N-succinimidyl citrate.[8] It should be noted that we obtained a material of identical ^{1}H NMR, but with a much higher mp than that reported for the 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate, by repeated fractionation of the partially soluble diester from boiling chloroform. 2-*tert*-Butyl 1,3-di-*N*-succinimidyl citrate: mp 188-189 °C (lit. 167 °C); formula weight $C_{18}H_{22}N_2O_{11}$ (442.38). Anal. Calcd: C 48.87, H 5.01, N 6.33; found: C 48.75, H 5.00, N 6.28. Triethylamine (0.35 g, 3.47 mmol) was added dropwise to a mixture of 2-*tert*-butyl 1,3-di-*N*-succinimidyl citrate (0.1762 g, 0.3983 mmol) and N^{ϵ}-cinnamoyl-N^{ϵ}-hydroxy-L-lysine methyl ester, trifluoroacetic acid salt (6) (0.351 g, 0.8365 mmol) in 8.0 mL of dry dioxane at 15 °C under nitrogen. The solution was allowed to warm to room temperature and stirred overnight. TLC (8% EtOH/$CHCl_3$) showed all starting material was consumed. The solvents were removed under high vacuum, and column chromatography (6% EtOH/toluene) on LH-20 Sephadex (32 g) gave pure 7 as a colorless solid (230 mg, 70%) (with R_f = 0.42 in 9% EtOH/$CHCl_3$): ^{1}H NMR (d_6-DMSO/$CDCl_3$; 1:1 by volume) δ 8.12 (m, 2 H, NH), 7.52 (m, 4 H, aromatic), 7.47 (d, 2 H, olefinic), 7.32 (m, 6 H, aromatic), 7.18 (d, 2 H, olefinic), 4.25 (m, 2 H, CH), 3.62 (m, 10 H, CH_3 and CH_2NO), 2.60 (m, 4 H, CH_2), 1.63 (m, 8 H, CH_2), 1.35 (s, 9 H, *tert*-butyl), 1.34 (m, 4 H, CH_2); mass spectrum (FAB) M + 1 = 826, $C_{42}H_{56}N_4O_{13}$ (824.92). Anal. Calcd: C 61.15, H 6.84, N 6.79; found: C 60.89, H 6.95, N 6.60.

Nannochelin A (8). TFA (2 mL) was added dropwise to 7 (137 mg, 0.166 mmol) at 0 °C. After the addition was complete, the solution was allowed to warm to room temperature and stir for 1 h. TLC (9% EtOH/$CHCl_3$) showed no starting material remained after 1 h. The volatiles were removed under high vacuum and gave 169 mg of a crude oil. This colorless oil was eluted on LH-20 Sephadex (4.0 g) with 7% EtOH/toluene to give 102 mg (80%) of nannochelin A as a white solid (mp 88-89 °C): ^{1}H NMR (d_6-DMSO/$CDCl_3$ (1:1)) δ 9.75 (s, 1 H, COOH), 8.19 (d, 1 H, NH), 8.13 (d, 1 H, NH), 7.52 (d, 4 H, aromatic), 7.46 (d, 2 H, J^3_{H-H} = 15.9 Hz, olefinic), 7.31 (m, 6 H, aromatic), 7.18 (d, 2 H, J^3_{H-H} = 15.9 Hz, olefinic), 4.25 (m, 2 H, CH), 3.60 (m, 4 H, CH_2NO), 3.59 (s, 6 H, OCH_3), 2.62 (m, 4 H, CH_2), 1.62 (m, 8 H, CH_2), 1.30 (m, 4 H, CH_2); ^{13}C NMR (CD_3OD) δ 22.29, 25.78, 30.57, 30.66, 42.96, 43.30, 51.29, 52.05, 52.09, 73.68, 116.20, 127.59, 128.53, 129.52, 135.11, 142.33, 142.37, 170.54, 170.89, 172.63, 175.19; mass spectrum (negative FAB) M^+ = 768, $C_{38}H_{48}N_4O_{13}$ (768.82) UV spectrum λ_{max} = 280 nm (lit. 280 nm); IR (KBr pellet) 3272, 2954, 2862, 1739, 1646, 1580, 1549, 1441, 1215, 980, 764 cm^{-1}; optical rotation $[\alpha]_D$ -12° (*c* 0.65, MeOH, 26 °C) (lit. $[\alpha]_D$ -13° (*c* 0.9, MeOH, 25 °C)); TLC (SiO_2) R_f = 0.1 (10% MeOH/CH_2Cl_2) matches lit. value.[11] Anal. Calcd: C 59.37, H 6.29, N 7.29; found: C 59.13, H 6.35, N 7.21.

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C-2 Dimethyl *seco*-Mevinic Acids. Synthesis of Monocyclic HMG-CoA Reductase Inhibitors from (*R*)-(-)-Carvone

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An efficient preparation of novel monocyclic HMG-CoA reductase inhibitors from (*R*)-(-)-carvone is reported. Utilizing this chiral carbon pool, the C-2 dimethyl *seco*-mevinic acid **3a** was prepared in 17 steps and 5.2% overall yield. The key chiral intermediate aldehyde **10a** was prepared via a short and efficient synthetic sequence (six steps, 27% yield) from (*R*)-(-)-carvone. The appropriate chirality of the diol acid side chain was secured by employing the chiral acetate synthon "(*S*)-HYTRA" and by performing a stereoselective 1,3-syn reduction on the β-hydroxy ketone **19**. Structural requirements at the C-2 position are rather stringent, and deletion of or addition of an extra methyl group are both unacceptable modifications for this novel class of monocyclic HMG-CoA reductase inhibitors.

Introduction

Hypercholesterolemia is considered to be a major risk factor for coronary heart and artery disease, which is a leading cause of deaths in the United States.[1] In humans, more than half of the total body cholesterol is derived from de novo biosynthesis.[2] Thus, pharmacological intervention of this endogeneous pathway has become a popular and logical approach for reducing total plasma cholesterol levels.[3] While the cholesterol biosynthetic pathway involves more than 25 different enzymatic transformations, inhibition at key regulatory sites would be expected to produce the most profound effect. In this regard, inhib-

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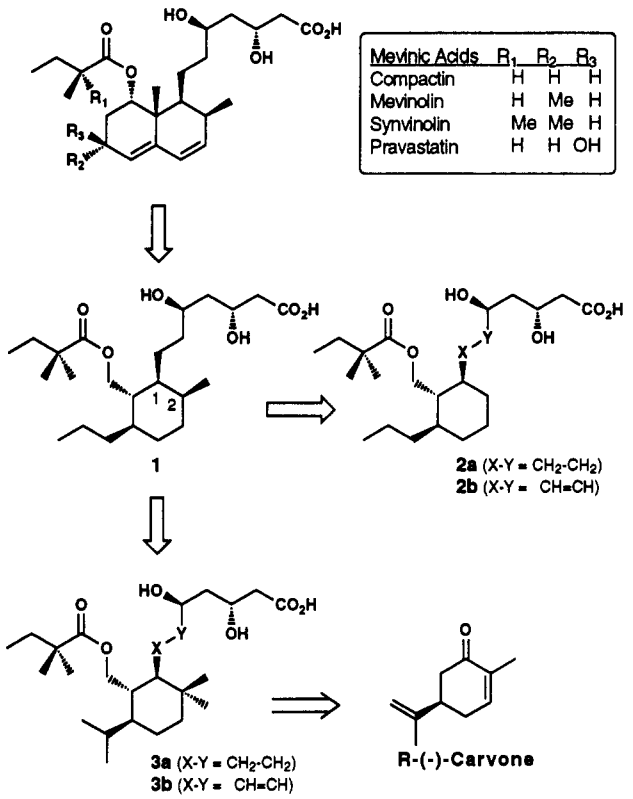
(1) Goldman, L. *Hosp. Practice* **1980**, *207*, 433-446.
(2) Grundy, S. M. *West. J. Med.* **1978**, *128*, 13-25.
(3) Lee, T.-J. *TIPS* **1987**, *8*, 442-446.

0022-3263/92/1957-7143$03.00/0

itors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which is the major rate limiting enzyme in the cascade, have attracted the greatest attention.[4]

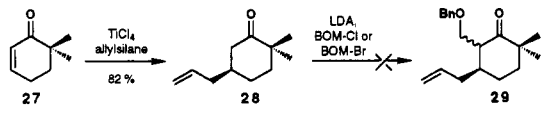
The fungal metabolite compactin was isolated in 1976 and found to be a potent HMG-CoA reductase (HMGR) inhibitor.[5] This was soon followed by the discovery of structurally related natural products mevinolin (generic name, Lovastatin) and Pravastatin, which have been shown to be effective in lowering plasma cholesterol in various animal models and in humans, and are being currently marketed as therapeutic agents for the treatment of hypercholesterolemia.[6] In our research program directed toward the discovery of improved HMGR inhibitors, *seco*-mevinic acid (1) was recently identified as a novel lead.[7] Compound 1 was prepared in 26 steps from pravastatin and was found to have an I_{50} value of 8 nM. While the remarkable in vitro potency of this structurally new class of HMGR inhibitors warranted further investigation, the high degree of synthetic complexity associated with preparation of 1 and its related analogs was a limiting factor. In an attempt to obviate this problem, we recently designed an efficient and flexible synthesis of desmethyl analogs **2a,b** of 1.[8] Unfortunately, the desmethyl analog **2a** was 100-fold less active than 1, thereby curtailing our plans for a rapid structure–activity relationship (SAR) study in the seco series. This result highlighted the critical requirement of a substituent at the C-2 position, suggesting that it was probably involved in orienting the diol acid side chain in an appropriate conformation and/or it participated in important hydrophobic interactions in that region of the molecule. With this hypothesis in mind, we reasoned that a dimethyl analog would be a more suitable target since it preserved the crucial axial methyl group at the C-2 position and yet eliminated chirality from that center, thereby simplifying the synthesis and fulfilling our objective of facilitating SAR study of this important class of HMGR inhibitors. Instead of choosing the direct dimethyl analogs of seco acids **2a,b**, we opted to prepare compounds **3a,b**. These were preferred because retrosynthetic analysis revealed the possibility of utilizing readily available (*R*)-(−)-carvone (Aldrich) as an appropriate starting material for their syntheses. Thus, if successful, this strategy would enable us to conveniently prepare **3a,b** and other structurally related analogs in homochiral form. Because of this choice, an additional difference between the C-2 dimethyl analog **3** and the lead compound 1 was that the *n*-propyl group at C-5 position was now substituted by an isopropyl group. However, based on other studies,[9] this was expected to have minimal effect on overall activity. In this paper, we give a full account of our efforts toward the successful execution of this idea and briefly discuss the biological activity of **3a,b** and their implications in terms of our overall understanding about the critical structural requirements for this novel class of HMGR inhibitors.



Chemistry

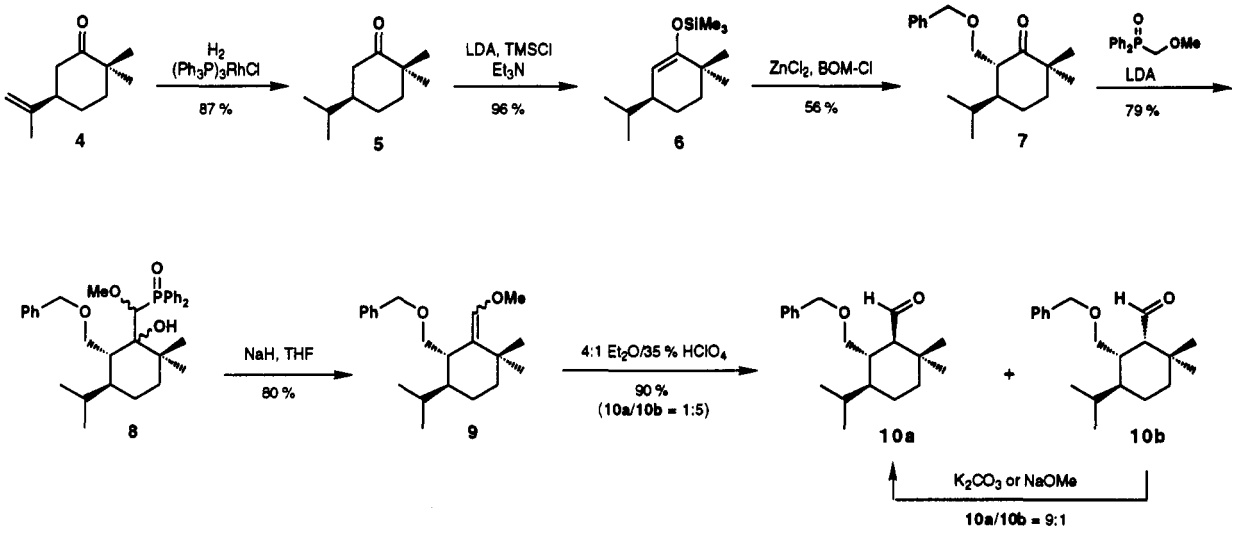
The chiral dimethyl ketone **4** was prepared according to literature procedure in 95% yield by reductive alkylation of (*R*)-(−)-carvone using K-Selectride (Aldrich) and iodomethane.[10] To avoid complications during the final steps of the synthesis, it was decided to reduce the isoprenyl side chain at any early stage. Thus, hydrogenation of **4** using Wilkinson's catalyst gave the fully saturated ketone **5**. Direct alkylation of the lithium enolate of **5** was not attempted because it was expected to be problematic based on previous experience with structurally similar ketones.[11] Alternatively, Lewis acid mediated alkylation[12] of **5** via the corresponding silyl enol ether **6** proceeded smoothly and in a stereoselective manner (trans:cis = >9:1) to provide the desired, *trans*-benzyl ether **7** (J_{Ha}–J_{Hb} = 11.14 Hz) in 53.8% overall yield from **5**. The next requirement was conversion of ketone **7** to the one-carbon homologated aldehyde **10a**. While numerous reagents are available for such a synthetic transformation, we had previously encountered best results with the Wittig reagent methoxymethylenetriphenylphosphorane ($MeOCH{=}PPh_3$) during a similar homologation in the preparation of the desmethyl analogs **2a,b**.[8] Unfortunately, this reagent was found to be unsuccessful with the hindered dimethyl ketone **7**.[13]

(4) Roth, B. D.; Sliskovic, D. R.; Trivedi, B. K. *Annual reports in Medicinal Chemistry*; Allen, R. C., Ed.; Academic Press: San Diego, CA, 1989; Vol. 24, pp 147–156.
(5) (a) Endo, A.; Kuroda, M.; Tsujita, Y. *J. Antibiotic* **1976**, *29*, 1346. (b) Endo, A. *Trends Biochem. Sci.* **1981**, *6*, 10.
(6) (a) Hoeg, J. M.; Brewer, H. B. *J. Am. Med. Assoc.* **1987**, *258*, 3532–3536. (b) Grundy, S. M. *N. Eng. J. Med.* **1988**, *319*, 24–31.
(7) Karanewsky, D. S. *Tetrahedron Lett.* **1991**, *32*, 3911.
(8) Patel, D. V.; Gordon, E. M. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 509–512.
(9) Additional studies conducted on the lead compound 1 by Dr. D. S. Karanewsky at Bristol-Myers Squibb have indicated greater flexibility and tolerance to structural variations in that region of the molecule. These results will be published elsewhere in the near future.
(10) Fortunato, J. M.; Ganem, B. *J. Org. Chem.* **1976**, *41*, 2194.
(11) (a) For example, the lithium enolate of ketone **28** failed to react directly with (benzyloxy)methyl chloride or bromide. **28** was prepared by conjugate allylation of 6,6-dimethyl-2-cyclohexen-1-one (**27**) under Sakurai conditions.[11b] Similar alkylation attempts with ketone **4** were also unsuccessful.



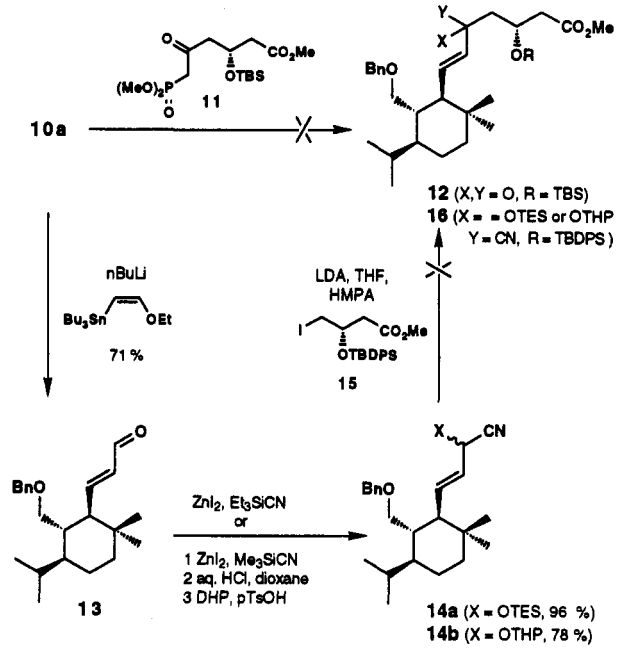
(b) Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* **1977**, *99*, 1673.
(12) (a) Brownbridge, P. *Synthesis* **1983**, 85. (b) Reetz, M. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 96.

Scheme I



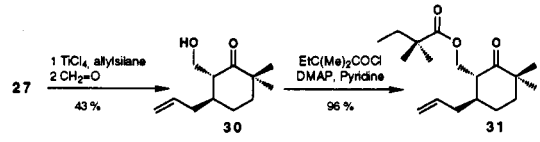
Alternatively, we turned our attention to the phosphine oxide reagent $MeOCH_2P(O)Ph_2$ whose anion is sterically less demanding and also more nucleophilic compared to the phosphorane $MeOCH{=}PPh_3$.[14] Thus, treatment of $MeOCH_2P(O)Ph_2$ with LDA in THF gave the lithio anion which reacted smoothly with ketone **7** at −78 °C to provide the hydroxyphosphinyls **8** as a mixture of diastereomers in 79% overall yield. In the literature, it has been recommended to isolate the hydroxyphosphinyls and then convert them to their sodium salts for effecting their elimination to the corresponding vinyl ethers.[14] Indeed, upon treatment of **8** with sodium hydride in THF, the vinyl ether **9** was obtained as an *E*/*Z* mixture in 80% yield. In this particular instance, we later found that the corresponding lithium alkoxides also successfully underwent the desired transformation under appropriate conditions. Thus, **9** could be directly obtained from ketone **7** simply by warming the crude reaction mixture of the Wittig reaction to room temperature and stirring it for 48 h. This eliminated the need for chromatographically isolating the intermediate diastereomeric hydroxyphosphinyls **8** and also improved the yield slightly for the overall transformation of ketone **7** to the enol ether **9** (72%). While hydrolysis of **9** to the dimethyl aldehydes **10a,b** was straightforward and proceeded in essentially quantitative yields, this epimeric mixture was nonseparable, enriched in the undesired axial epimer **10b**, and could not be equilibrated under the standard acidic conditions.[15] These observations were in sharp contrast to the experience we had shared with a similar type of aldehyde during the preparation of desmethyl analogs **2a,b**.[8] Even under basic conditions, no epimerization was observed with triethylamine or DBU in acetonitrile, but fortunately, clean equilibration in the desired direction was finally accomplished employing K_2CO_3 or NaOMe (**10a/10b** >9:1). This constitutes a short and efficient synthesis of the chiral aldehyde **10a** from (*R*)-(−)-carvone (six steps, 27% yield). The entire sequence can be conveniently scaled up since the early intermediates are easily purified by distillations, the trans ketone **7** being the first intermediate requiring chromatographic purification.

Scheme II



The stage was now set for trying the crucial β-keto phosphonate coupling reaction. This reaction, while expected to be sensitive to the steric environment around the ketone group, had worked reasonably well in the desmethyl series.[8] To our dismay, the reaction failed to proceed with the dimethyl aldehyde **10a** under the standard conditions. Simple, recently reported variations of similar couplings (LiBr, Et_3N, CH_3CN[16] or LiCl, DBU, CH_2Cl_2, −10 °C[17]) and additional modifications[18] were

(13) Wittig olefination attempts utilizing $MeOCH{=}PPh_3$ with α,α′-substituted ketone **31**, prepared as shown below, were also found to be unsuccessful.



(14) Earnshaw, C.; Wallis, C. J.; Warren, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3099.

(15) Some of the acidic conditions under which epimerization was attempted were (a) 4:1 Et_2O/35% $HClO_4$, (b) pTsOH in CH_2Cl_2, and (c) Pyr^+OTs^- in EtOH.

(16) Heathcock, C. H.; Davis, B. R.; Hadley, C. R. *J. Med. Chem.* **1989**, *32*, 197.

Scheme III

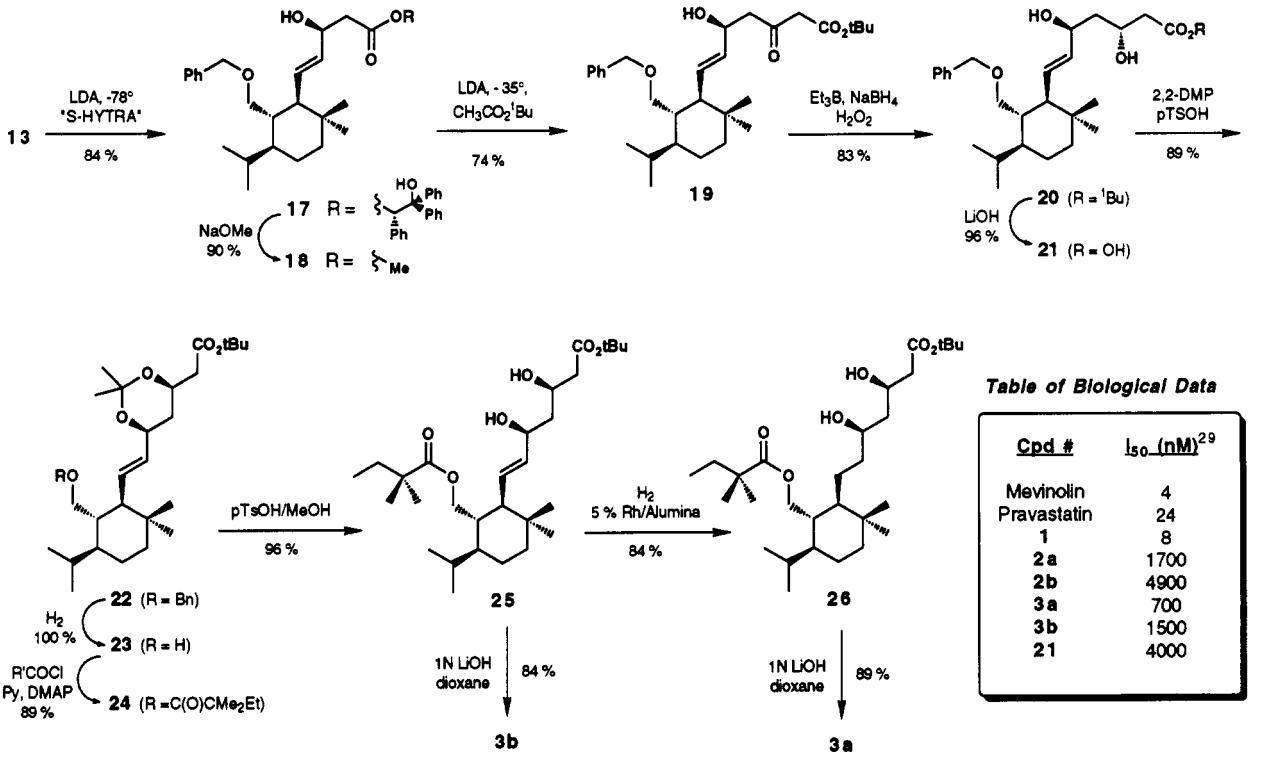


Table of Biological Data

Cpd #	I_{50} (nM)[29]
Mevinolin	4
Pravastatin	24
1	8
2a	1700
2b	4900
3a	700
3b	1500
21	4000

attempted but met with no success. The failure of this highly convergent coupling forced us to adopt a linear route for the synthesis of targeted dimethyl analogs **3a,b**. In that respect, stepwise homologation of the aldehyde **10a** to the enone **13** was unsuccessful with the Wittig reagent triphenylphosphoranylidene acetaldehyde,[19] but it reacted efficiently with *cis*-2-ethoxyvinyllithium[20] to afford **13** in 71% yield after workup. An important feature was that no epimerization was observed even when excess reagent was used to drive the reaction to completion. Even when an epimeric mixture of aldehydes **10ab** was employed in the reaction, the resulting enone could be easily equilibrated under basic conditions (NaOMe, MeOH) to afford the desired equatorial epimer. At this stage, we had the option of reacting **13** directly with the dianion of methyl acetoacetate, but this approach would render the upper side chain of the molecule racemic and was therefore not pursued. Amongst several approaches for a chiral synthesis of the diol acid moiety,[21] we opted to convert **13** to the corresponding cyano ether and then react it with the chiral iodide **15**.[22] As shown in Scheme II, while the THP-protected and triethylsilyl-protected cyano ethers were prepared in very good yields, both failed to react with iodide **15**.

Finally, we turned our attention to "(*S*)-HYTRA" ((*S*)-(−)-2-hydroxy-1,2,2-triphenylethyl acetate),[23] an excellent reagent originally developed by Braun[24] which has found extensive use and success[25] recently as a chiral acetate reagent. In our hands, reaction of (*S*)-HYTRA at −78 °C with the enone **13** using LDA as a base yielded the hydroxy ester **17**[26] in 84% yield. Compound **17** was transesterified, and the resulting methyl ester **18** reacted smoothly with lithio-*tert*-butyl acetate at −35 °C to yield the keto ester **19** in 74% yield. The well-precedented stereoselective 1,3-syn reduction of **19** gave the diol **20**.[27] It is important to realize that although the final target molecules **3a,b** have an ester side chain at the C-5 position, the diol **20** bears a benzyloxy group at that position. If the desired ester side chain could be incorporated at an early stage in the synthesis, functional group manipulations and transformations toward the end of the sequence could be avoided. This was especially appealing in view of the fact that the chemistry involved in the conversion of aldehyde **10a** to diol **20** seemed compatible with the presence of the desired ester side chain at C-5. This possibility was investigated but found to be unrewarding, forcing us to continue our synthesis with the diol **20**.[28] In order to

(17) Picard, J. A.; Sliskovis, D. R.; Roth, B. D.; Shaw, M. K.; Ferguson, E.; Krause, B. R.; Newton, R. S. *198th ACS Meeting, Miami Beach, FL* Sept 10–15, 1989.

(18) (a) LiCl, DBU, CH_3CN, rt to reflux. (b) K_2CO_3, 18-crown-6. (c) KHMDS, 18-crown-6.

(19) (a) Trippett, S.; Walker, D. M. *J. Chem. Soc.* **1961**, 2130. (b) Bestmann, H. J.; Vostrowsky, O.; Paulus, H.; Billmann, W.; Stransky, W. *Tetrahedron Lett.* **1977**, 121.

(20) (a) Wollenberg, R. H.; Albizati, K. F.; Peries, R. *J. Am. Chem. Soc.* **1977**, *99*, 7365. (b) Leusink, A. J.; Buddinh, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285.

(21) (a) Johnson, W. S.; Kelson, A. B.; Elliott, J. D. *Tetrahedron Lett.* **1988**, *29*, 3757. (b) Sletzinger, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M.-H. *Tetrahedron Lett.* **1985**, *26*, 2951.

(22) (a) Karanewsky, D. S.; Madia, M. C.; Ciosek, C. P., Jr.; Robl, J. A.; Sofia, M. J.; Simpkins, L. M.; Delange, B.; Harrity, T. W.; Biller, S. A.; Gordon, E. M. *J. Med. Chem.* **1990**, *33*, 2952–2956. (b) Robl, J. A.; Duncan, L. A.; Pluscec, J.; Karanewsky, D. S.; Gordon, E. M.; Ciosek, C. P. Jr.; Rich, L. C.; Dehmel, V. C.; Slusarchyk, D. A.; Harrity, T. W.; Obrein, K. A. *J. Med. Chem.* **1991**, *34*, 2804–2815.

(23) The reagents (*S*)-HYTRA and (*R*)-HYTRA are now commercially available from Aldrich Chemical Co. and Chiron Laboratories (Davos Chemical Corporation, NJ).

(24) Mahler, U.; Devant, R. M.; Braun, M. *Chem. Ber.* **1988**, *121*, 2035.

(25) (a) Devant, R. M.; Mahler, U.; Braun, M. *Chem. Ber.* **1988**, *121*, 397. (b) Baader, E.; Bartmann, W.; Beck, G.; Below, P.; Bergmann, A.; Jendralla, H.; Kesseler, K.; Wess, G. *Tetrahedron Lett.* **1989**, *30*, 5115. (c) Lynch, J. E.; Volante, R. P.; Wattley, R. V. Shinkai, I. *Tetrahedron Lett.* **1987**, *28*, 1385.

(26) Compound **17** appeared to be essentially one isomer by ^1H NMR and ^{13}C NMR. Although the exact % ee was not determined via preparation of the Mosher ester of a suitable intermediate like **18**, the presence of the other diastereomer was not detected in any of the subsequent steps leading to the final targets **3a,b**.

(27) (a) Narasaka, K.; Pai, F.-C. *Tetrahedron* **1984**, *40*, 2233. (b) Kathawala, F. G.; Prager, B.; Prasad, K.; Repic, O.; Shapiro, M. J.; Stabler, R. S.; Widler, L. *Helv. Chim. Acta* **1986**, *69*, 803.

substitute the benzyl side chain in **20** with the desired acyl group, the diol functionality was first protected as its acetonide, best results being achieved with 2,2-dimethoxypropane instead of the more reactive 2-methoxypropene. At this stage, it was gratifying to realize that closely monitored hydrogenolysis of **22** using Pearlmans catalyst resulted in very clean debenzylation without affecting the double bond at all, since this would now enable us to prepare the dimethyl analogs with both the saturated and unsaturated linkers. Acylation of **23** was uneventful, and deprotection of the acetonide group in **24** was best achieved by treatment with *p*-toluenesulfonic acid in methanol. It was rather surprising that hydrogenation of **25** turned out to be slightly problematic. When 10% Pd/C was used as the catalyst, the desired hydrogenation was accompanied by hydrogenolysis of the allylic alcohol as well as olefin isomerization. While the situation did not improve upon switching to 10% Pt/C, these side reactions were reduced to a minimum when the reaction was conducted in ethyl acetate and rhodium on alumina was employed as the catalyst. Hydrolysis of the *tert*-butyl esters **25** and **26** was slow but clean and afforded the final compounds **3b** and **3a** with unsaturated and saturated linkers, respectively, in high yields. Similarly, hydrolysis of intermediate **20** provided the simple benzyl side chain bearing analog **21**. In summary, the complete, chiral synthesis of the dimethyl analog **3a** was accomplished in 17 steps and 5.2% overall yield from (*R*)-(−)-carvone.

Discussion

Compounds **21**, **3a**, and **3b** were tested for their ability to inhibit the conversion of ^{14}C-HMG-CoA to ^{14}C-mevalonic acid catalyzed by partially purified rat microsomal HMG-CoA reductase.[29] The saturated dimethyl analog **3a** was 90-fold less active than the parent compound **1**. When compared to the desmethyl analog, only modest improvement in potency was realized upon introduction of a *gem*-dimethyl substituent at the C-2 position (**2a** vs **3a**). While the desmethyl analog made us realize the importance of a substituent at the C-2 position (**2a** vs **1**), the result of the dimethyl analog reinforces the previous finding and illustrates the strict requirements around that position of the molecule (**1** vs **3a**). Having an axially oriented methyl group at the C-2 position is not the only specific requirement for good potency, but it is also equally important not to have any C-2 substitution in the equatorial position. The extra equatorial methyl group in the dimethyl analog **3a** must be preventing one or both of the critical oxygenated side chains (the ester and the diol acid moieties) from adopting a conformation necessary for good binding. The unsaturated analog **3b** was equipotent or slightly less active than the saturated analog **3a**, a trend that was also observed in the desmethyl series (**2a** vs **2b**).[8] Compound **21**, the dimethyl analog with the benzyl ether side chain in place of the ester side chain, also displayed only modest levels of activity. These results coupled with our previous findings[8] led us to the following conclusions regarding the *seco*-mevinic acid based HMG CoA inhibitors: (a) all four substituents around the cyclohexyl ring are required for efficient binding to and inhibition of HMG CoA reductase, and (b) the C-2 position of these inhibitors is highly sensitive and exhibits strict structural requirements. Modifications such as the deletion of a methyl group or addition of an extra methyl group are both deleterious to the overall activity of these molecules.

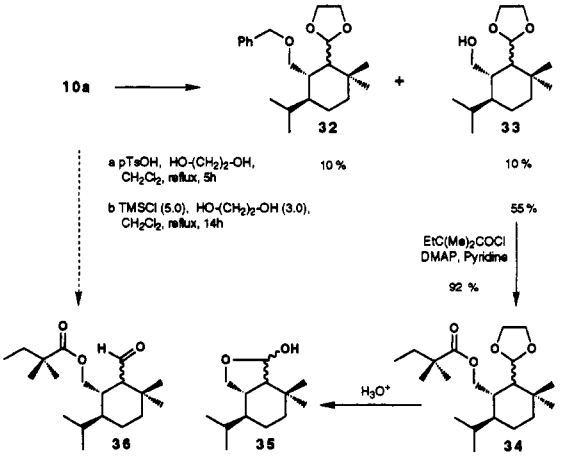
Summary

The *seco*-mevinic acids are a novel but synthetically complex class of HMG-CoA reductase inhibitors.[7,8,16] In an attempt to facilitate rapid SAR study required to get a timely assessment of their true potential in terms of drug development, we had previously developed an efficient and flexible synthesis of the desmethyl analog **2a** of the original lead composition **1**.[8] A 100-fold loss in activity of the desmethyl analog clearly dictated the importance of a substituent at the C-2 position. Continuing our search for an inhibitor that would be more amenable to developmental work, we next embarked on the synthesis of a dimethyl analog of **1**. This strategy was even more appealing since it enabled us to make use of the chiral carbon pool for initiating the construction of chiral centers in the molecule.[30] Starting from (*R*)-(−)-carvone (Aldrich), we prepared the dimethyl analog **3a** (17 steps, 5.2% overall yield) and related analogs **3b** and **21**. The key chiral intermediate aldehyde **10a** was prepared via a short and efficient synthetic sequence (six steps, 27% yield) from (*R*)-(−)-carvone. The appropriate chirality of the diol acid side chain was secured by utilizing the chiral acetate synthon (*S*)-HYTRA and by performing a stereoselective 1,3-syn reduction on the β-hydroxy ketone **19**. Structural requirements at the C-2 position are rather stringent, and deletion of or addition of an extra methyl group are both unacceptable modifications for this novel class of HMG-CoA reductase inhibitors.

Experimental Section

General. All reactions were carried out under a positive pressure of dry argon, unless otherwise specified. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium or potassi-

(28) Since the inert benzyloxy side chain was a critical requirement for Wittig homologation of ketone **7**, aldehyde **10a** would be the earliest intermediate where it could be substituted by the ester side chain. Simple acetalization of **10a** was rather tricky, problems mainly arising from participation of the neighboring benzyloxy group. We manipulated this to our advantage and derived conditions (TMSCl, ethylene glycol) where acetalization and debenzylation were simultaneously achieved to provide the alcohol **33** in 55% yield. Acylation of **33** afforded the ester **34** but removal of the acetal group from **34** was unsuccessful under a wide variety of conditions, the only isolable product being the lactol **35** instead of the aldehyde **36**.



(29) An I_{50} value reflects the amount of compound required for 50% inhibition of the enzyme under the standard assay conditions. A detailed description of the assay can be found in ref 22.

(30) Researchers at Sandoz Inc. have recently disclosed the preparation and activity of several cyclohexyl-based monocyclic HMG CoA reductase inhibitors. Interestingly, they have also employed (*R*)-(−)-carvone as a starting material to prepare two *seco*-mevinic acid analogs. However, the retrosynthetic orientations are very different, and unlike our synthesis, they have utilized it to derive an isopropyl substituent at the C-2 position. See: Damon, R. E.; Coppola, G. M.; Vedananda, T. *200th National Meeting of the American Chemical Society*; Aug 26–31, 1990, Washington, D.C.

um/benzophenone ketyl prior to use. Acetonitrile, benzene, dichloromethane, diisopropylamine, hexane, methanol, pyridine, and toluene were distilled from calcium hydride prior to use.

TLC was performed using EM Science (E. Merck) 5- × 10-cm plates precoated with silica gel 60 F_{254} (0.25-mm thickness), and the spots were visualized by any of the following methods: UV, iodine, phosphomolymdic acid (PMA), ceric ammonium sulfate, anisaldehyde or vanillin stain. EM Science's silica gel 60 (230–400 mesh ASTM) was used for flash chromatography. A ratio of 25–100:1 silica gel/crude product by weight and a nitrogen pressure of 5–25 psi was normally employed for flash columns. Reversed-phase chromatographic purification of final compounds was carried out using CHP20P gel, a 75–150-μm polystyrene–divinyl benzene copolymer purchased from Mitsubishi Chemical Industries.

Melting points were determined on an electrothermal Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on one of the following instruments: JOEL GX-400 operating at 400 MHz (^{1}H) or 100 MHz (^{13}C), JOEL FX-270 operating at 270 (^{1}H) or 67.8 (^{13}C) MHz, and JOEL FX-60Q operating at 15 MHz (^{13}C). Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), and coupling constants (J) are in hertz (Hz). IR spectra were recorded on a Mattson Sirius 100 FT-IR spectrophotometer, and the absorption maxima are reported in cm^{-1}. Mass spectra were recorded on a Finnigan MAT TSQ-4600 mass spectrometer (chemical ionization, CI) or a VG-ZAB-2F mass spectrometer (fast atom bombardment, FAB). High-resolution mass spectra (HRMS) were determined using peak-matching techniques versus PEG standards on a VG-ZAB-2F spectrometer. Optical rotations were measured using a Perkin-Elmer Model 241 polarimeter and a 10-cm path length optical cell. Microanalysis results were adjusted to obtain the best fit assuming nonstoichiometric hydration.

Preparation of 5. Tris(triphenylphosphine)rhodium chloride (0.1 g, 0.11 mmol, 0.0001 equiv) was added to a solution of **4**[10] (11.6 g, 69.9 mmol, 1.0 equiv) in toluene (250 mL) and was placed on a Parr hydrogenator until the theoretical amount of H_2 was taken up. The solution was then filtered through Celite and concentrated under vacuum to give the crude product. Vacuum distillation afforded pure **5** (89–91 °C (4.25 mmHg), 10.2 g, 87%). MS: $(M + H)^+$ 169, $(M + NH_4)^+$ 186. ^{1}H ($CDCl_3$): 0.89 (d, 3 H, J = 6.4), 0.90 (d, 3 H, J = 5.8), 1.05 (s, 3 H), 1.14 (s, 3 H), 1.4–1.85 (br m, 6 H), 2.27 (m, 2 H).

Preparation of 6. n-Butyllithium (1.6 M, 45 mL, 72 mmol, 1.2 equiv) was added dropwise to a solution of diisopropylamine (10.93 mL, 78 mmol, 1.3 equiv) in THF (250 mL) at −78 °C. After complete addition, it was stirred for an additional 15 min at −78 °C, warmed to −5 °C, stirred for 5 min, and then recooled to −78 °C. A solution of **5** (10.11 g, 60 mmol, 1.0 equiv) in THF (10 mL) was added dropwise at −78 °C after which the reaction mixture was stirred at −15 °C for 15 min and then recooled to −78 °C. A centrifuged mixture of TMSCl (19 mL, 150 mmol, 2.5 equiv) and TEA (12.5 mL, 90 mmol, 1.5 equiv) was then added at −78 °C. After being stirred for 1 h at −78 °C, the reaction mixture was quenched with water (30 mL), warmed to room temperature, and extracted with ether (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by vacuum distillation to afford **6** (79–82 °C (1.75 mmHg), 13.9 g, 96%). MS: $(M + H)^+$ 241, $(M - CH_4)^-$ 225. ^{1}H ($CDCl_3$): 0.28 (s, 9 H), 0.95 (d, 3 H, J = 6.5), 0.97 (d, 3 H, J = 7), 1.08 (s, 3 H), 1.1 (s, 3 H), 1.25–1.75 (br m, 5 H), 2.07 (m, 1 H), 4.68 (d, J = 2.3).

Preparation of 7. (Benzyloxy)methyl chloride (30.4 mL, 0.219 mol, 1.2 equiv) was added to a solution of **6** (43.7 g, 0.182 mol, 1.0 equiv) in dichloromethane (500 mL) at −78 °C followed by addition of $ZnCl_2$ (1 M in diethyl ether, 183 mL, 0.183 mol, 1.0 equiv). After being stirred for 2.5 h at −78 °C the reaction was quenched with water (400 mL) and warmed to room temperature. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 30:1 petroleum ether–diethyl ether) to afford **7** (29.5 g, 56%). TLC: R_f = 0.22 (9:1 petroleum ether/diethyl ether, visualization by UV, PMA). MS: $(M + H)^+$ 289. IR: (neat) C=O 1707.1 cm^{-1}. ^{1}H ($CDCl_3$): 0.86 (d, 3 H, J = 6.5), 0.93 (d, 3 H, J = 7), 1.06 (s, 3 H), 1.14 (s, 3 H), 1.5–2.0 (m, 6 H), 2.63 (ddd, J = 11.1, 4.1), 3.68 (dd, 1 H, J = 9.9, 4.7), 3.71 (dd, 1 H, J = 9.9, 3.5), 4.50 (d, 1 H, J = 12.3), 4.54 (d, 1 H, J = 12.3), 7.2–7.4 (m, 5 H). ^{13}C ($CDCl_3$): 15.3, 19.5, 21.3, 25.0, 25.5, 27.7, 39.4, 44.5, 46.5, 49.4, 66.3, 73.2, 127.2, 127.4, 128.1, 138.7, 215.2. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.79. Found: C, 79.39; H, 9.96.

Preparation of 8. n-Butyllithium (1.6 M, 20.8 mL, 33.3 mmol, 3.2 equiv) was added dropwise to a solution of diisopropylamine (4.8 mL, 34.3 mmol, 3.3 equiv) in THF (100 mL) at −78 °C. After complete addition, the reaction mixture was stirred for an additional 15 min at −78 °C, warmed to −5 °C and stirred for 5 min and then recooled to −78 °C. Methoxymethyldiphenylphosphine oxide (7.68 g, 31.2 mmol, 3.5 equiv), prepared according to literature procedure[14] was added portionwise at −78 °C. After complete addition the reaction mixture was warmed to −5 °C for 20 min and then recooled to −78 °C. A solution of **7** (3.0 g, 10.4 mmol, 1.0 equiv) in THF (5 mL) was added dropwise over 20 min. After being stirred for 3.5 h at −78 °C, the reaction mixture was quenched with water (50 mL), warmed to room temperature, and extracted with ethyl acetate (3 × 80 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 3:1 hexane/ethyl acetate) to afford **8** (4.44 g, 79%). TLC: R_f = 0.38 (3:1 hexane/ethyl acetate, visualization by UV, PMA). MS: $(M + H)^+$ 535, $(M - H)^-$ 533. IR: (KBr) P=O 1178 cm^{-1}. $[\alpha]_D$ = +18.86° [c = 1.89, MeOH]. ^{1}H ($CDCl_3$): 0.73 (d, 3 H, J = 7), 0.77 (s, 3 H), 0.87 (d, 3 H, J = 7), 0.94 (s, 3 H), 1.0–2.0 (m, 7 H), 3.01 (s, 3 H), 3.63 (dd, 1 H, J = 9.9, 2.0), 4.15 (d, 1 H, J = 9.9), 4.26 (d, 1 H, J = 11.7), 4.44 (d, 1 H, J = 2.3), 4.76 (d, J = 11.7), 5.0 (s, 1 H), 7.2–8.0 (m, 15 H). Anal. Calcd for $C_{33}H_{43}O_4P$: C, 74.13; H, 8.11; P, 5.79. Found: C, 73.98; H, 7.96; P, 6.07.

Preparation of 9. Phosphine oxide adduct **8** (3.5 g, 6.6 mmol, 1.0 equiv) in THF (5 mL) was added dropwise to NaH (60%, 4.15 g, 104 mmol, 15 equiv, prewashed with hexane (3 × 50 mL)) in THF (150 mL) at 0 °C and the mixture warmed to room temperature and stirred for 16 h. The reaction mixture was then recooled to 0 °C, quenched with water (50 mL), and extracted with ethyl acetate (3 × 150 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 4:1 hexane/ethyl acetate) to afford the mixture of enol ethers **9** (1.67 g, 80%). **9** could also be obtained directly from **7** by warming the crude reaction mixture of the Wittig reaction of **7** to room temperature and stirring for 48 h, followed by usual workup and chromatographic purification (70% yield on a 50 mmol scale reaction). TLC: R_f = 0.70 (3:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + H)^+$ 317, $(M + NH_4)^+$ 334. IR: (neat, enol ether, 1651 cm^{-1}). $[\alpha]_D$ = +64.27° [c = 2.53, MeOH]. ^{1}H ($CDCl_3$): 0.86 (d, 3 H, J = 6.5), 0.94 (d, 3 H, J = 6.5), 0.97 (s, 3 H), 1.03 (s, 3 H), 1.0–1.75 (br m, 6 H), 3.37 (m, 1 H), 3.52 (s, 3 H), 3.67 (m, 1 H), 4.49 (d, 1 H, J = 12), 4.58 (d, J = 12), 5.93 (s, 1 H), 7.2–7.36 (m, 5 H). ^{13}C ($CDCl_3$): 20.0, 20.3, 21.5, 28.3, 30.4, 30.9, 32.6, 35.7, 36.1, 41.5, 59.2, 72.1, 73.9, 123.5, 127.1, 127.4, 128.1, 139.2, 143.4. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 80.09; H, 10.15.

Preparation of 10a. Perchloric acid (35%, 13 mL) was added to a solution of **9** (2.56 g, 8.1 mmol, 1.0 equiv) in diethyl ether (25 mL) and the resulting solution stirred at room temperature. After 3.5 h, water (50 mL) was added and the reaction mixture was extracted with diethyl ether (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The crude material was dissolved in THF (25 mL), and sodium methoxide in methanol (25%, 15 mL, 65.6 mmol, 8.1 equiv) was added at room temperature. After stirring 16 h, the reaction mixture was quenched with saturated NaCl solution (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 20:1 petroleum ether/diethyl ether) to afford a 9:1 mixture of **10a**/**10b** (2.17 g, 90%). TLC: R_f = 0.33 (9:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + H)^+$ 303, $(M + NH_4)^+$ 320. IR: (neat, C=O 1716 cm^{-1}). ^{1}H ($CDCl_3$): 0.81 (d, 3 H, J = 6.5), 0.90 (d, 3 H, J = 7), 0.98 (s, 6 H), 1.1–2.2 (m, 6 H), 2.02 (dd, 1 H, J = 4.7, 11.1), 3.24 (dd, 1 H, J = 6.4, 9.4), 3.53 (dd, 1 H, J = 2.9, 9.4), 4.37 (s, 2 H), 7.3 (m, 5

H), 9.6 (d, 1 H, J = 4.7). ^{13}C ($CDCl_3$): 15.3, 19.3, 20.7, 21.3, 26.8, 30.6, 33.4, 36.1, 41.5, 42.7, 62.3, 70.8, 73.1, 127.4, 127.6, 128.2, 138.0, 205.6. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.66; H, 10.28.

Preparation of 13. *n*-Butyllithium (1.6 M, 10.4 mL, 16.6 mmol, 2.5 equiv) was added to a solution of the tin reagent[20] (5.6 mL, 16.6 mmol, 2.5 equiv) in THF (50 mL) at −78 °C. After 1 h at −78 °C, a solution of **10a** (2.0 g, 6.6 mmol, 1.0 equiv) in THF precooled to −78 °C was added to the reaction mixture. After an additional 1 h at −78 °C, the reaction mixture was quenched with water (50 mL), warmed to room temperature, and extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 20:1 hexane/ethyl acetate) to afford **13** (1.53 g, 71%). TLC: R_f = 0.41 (9:1 hexane/ethyl acetate, visualization by UV, PMA). MS: $(M + H)^+$ 329, $(M + NH_4)^+$ 346. IR: (KBr) C=O 1689 cm^{-1}. $[\alpha]_D$ = +22.2° [c = 2.41, MeOH]. ^1H ($CDCl_3$): 0.76 (d, 3 H, J = 7), 0.83 (s, 3 H), 0.86 (s, 3 H), 0.92 (d, 3 H, J = 7), 1.0–1.65 (m, 6 H), 1.95 (m, 1 H), 2.30 (t, J = 10.5), 3.18 (dd, J = 9.6, 2.0), 3.44 (dd, J = 9.6, 2.6), 4.34 (s, 2 H), 6.09 (dd, 1 H, J = 15.8, 7.7), 6.59 (dd, 1 *H*, J = 15.8, 10.5), 7.2–7.35 (m, 5 H), 9.45 (d, 1 H, J = 7.7). ^{13}C ($CDCl_3$): 15.4, 19.5, 20.2, 21.4, 26.6, 31.2, 33.8, 39.4, 40.9, 42.2, 53.0, 68.4, 73.1, 127.5, 127.6, 128.2, 134.9, 138.3, 160.3, 193.5. Anal. Calcd for $C_{22}H_{32}O_2$: C, 80.19; H, 10.09. Found: C, 80.49; H, 10.35.

Preparation of 14a. A catalytic amount of ZnI_2 (5 mg, 0.015 mmol) was added to a solution of the aldehyde **13** (508 mg, 1.548 mmol) and Et_3SiCN (300 mg, 2.12 mmol, prepared according to Hertenstein et al. (Hertenstein, U. et al. *Chem. Ber.* **1980**, *113*, 3783) in THF (5 mL). After 15 min at rt, additional Et_3SiCN (500 mg, 3.54 mmol) and ZnI_2 (10 mg, 0.03 mmol) were added since a TLC check revealed the presence of some unreacted aldehyde. After an additional 15 min, the reaction was judged to be complete by TLC and the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). Drying and concentration gave the crude product which was purified quickly over a short column of silica gel by flash chromatography (30:1 hexane/ethyl acetate) to afford 698 mg (96%) of pure **14a**. TLC: R_f = 0.40 (9:1 hexane/ethyl acetate, visualization by PMA). ^1H ($CDCl_3$): 0.62–1.02 (m, 27 H), 1.22–1.53 (m, 7 H), 1.87–2.1 (m, 2 H), 3.25 (m, 1 H), 3.51 (m, 1 H), 4.3–4.45 (m, 2 H), 4.87 (m, 1 H), 5.45–5.57 (m, 1 H), 5.63–5.77 (m, 1 H), 7.25–7.33 (m, 5 H). HRMS calcd for $C_{29}H_{47}N_1O_2Si_1Na_1$: 492.3274; found $(M + Na)^+$ 492.3271. Anal. Calcd for $C_{29}H_{47}NSiO_2.0.5\ H_2O$: C, 72.69; H, 10.11; N, 2.92. Found: C, 72.74; H, 10.40; N, 2.87.

Preparation of 14b. A catalytic amount of ZnI_2 (5 mg, 0.015 mmol) was added to a solution of the aldehyde **13** (528 mg, 1.609 mmol) and TMSCN (300 μL, 2.25 mmol) in THF (5 mL). After 15 min at rt, additional TMSCN (500 μL, 3.75 mmol) and ZnI_2 (20 mg, 0.06 mmol) were added and the reaction was found to be complete after an additional 15 min. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (25 mL). Drying and concentration gave the crude cyano silyl ether (TLC: R_f = 0.62 in 4:1 hexane/ethyl acetate) which was treated with 1:1 dioxane/3 M aqueous HCl (10 mL) for 15 min. The reaction mixture was taken up in EtOAc (50 mL), washed sequentially with H_2O (1 × 30 mL) and saturated aqueous $NaHCO_3$ (1 × 30 mL), dried, and concentrated to afford the cyanohydrin (TLC: R_f = 0.26 in 4:1 hexane/ethyl acetate). The crude product was dissolved in CH_2Cl_2 (10 mL) and treated with 3,4-dihydro-2*H*-pyran (176 μL, 1.932 mmol) and pTsOH (361.4 mg, 1.9 mmol). After 30 min at rt, the reaction mixture was partitioned between CH_2Cl_2 (50 mL) and H_2O (25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), dried, and concentrated to give a residue which was purified by flash chromatography (9:1 petroleum ether/ether) to give 552 mg (78.1%) of **14b** as a complex mixture of diastereomers. TLC: R_f = 0.45 (3:1 petroleum ether/ether, visualization by PMA). ^1H ($CDCl_3$): 0.72–1.0 (m, 12 H), 1.15–1.81 (m, 12 H), 1.87–2.1 (m, 2 H), 1.95 (m, 1 H), 2.1 (m, 1 H), 3.2–3.8 (m, 4 H), 4.3–4.48 (m, 2 H), 4.9–5.05 (m, 2 H), 4.48–4.86 (m, 2 H), 7.24–7.36 (m, 5 H). HRMS calcd for $C_{28}H_{41}N_1O_3Na_1$: 462.2984; found $(M + Na)^+$ 462.2979.

Preparation of 17. *n*-Butyllithium (1.6 M, 8.0 mL, 12.8 mmol, 2.3 equiv) was added dropwise to a solution of diisopropylamine (1.97 mL, 14.0 mmol, 2.4 equiv) in THF (40 mL) at −78 °C. After complete addition the reaction mixture was stirred for 15 min, warmed to −5 °C for 15 min, and then recooled to −78 °C. (*S*)-HYTRA ((*S*)-(−)-2-hydroxy-1,2,2-triphenylethyl acetate, 1.93 g, 5.8 mmol, 1.0 equiv) was added in one portion, and the reaction mixture was stirred at −78 °C for 5 min, warmed to 0 °C for 30 min until the solution became clear, and recooled to −78 °C. A solution of **13** (1.91 g, 5.8 mmol, 1.0 equiv) in THF (25 mL) was added and the resulting solution stirred at −78 °C for 2 h. The reaction was then quenched with saturated NH_4Cl (60 mL) and HCl (3 N, 50 mL), warmed to room temperature, and extracted with ethyl acetate (4 × 65 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 5:1 hexane/ethyl acetate) to afford **17** (3.25 g, 84%). TLC: R_f = 0.44 (1:1 hexane/ethyl acetate, visualization by UV, PMA). MS: $(M + H - H_2O)^+$ 643, $(M + NH_4)^+$ 678. IR: (KBr) C=O 1734 cm^{-1}. Mp: 90–92 °C. ^1H ($CDCl_3$): 0.67–0.72 (m, 9 H), 0.89 (d, 3 H, J = 7.0), 1.05–1.47 (m, 5 H), 1.8–1.97 (m, 2 H), 2.2–2.42 (m, 3 H), 2.88 (s, 1 H), 2.87–2.9 (m, 1 H), 3.1 (dd, 1 H, J = 1.7, 9.4), 3.31 (dd, 1 H, J = 2.3, 9.4), 4.32 (s, 3 H), 4.28–4.36 (m, 1 H), 5.26–5.33 (m, 2 H), 6.72 (s, 1 H), 7.04–7.58 (m, 20 H). ^{13}C ($CDCl_3$): 15.4, 19.4, 20.1, 21.5, 26.7, 31.2, 33.0, 39.2, 40.9, 42.0, 42.4, 51.6, 68.3, 68.6, 72.8, 78.8, 80.2, 126.1, 126.2, 126.9, 127.2, 127.3, 127.4, 127.6, 127.8, 128.0, 128.2, 128.4, 132.6, 132.7, 135.5, 139.0, 142.5, 144.5, 170.5. Anal. Calcd for $C_{44}H_{52}O_5{\cdot}0.75H_2O$: C, 78.36; H, 8.00. Found: C, 78.48; H, 8.01.

Preparation of 18. Sodium methoxide in methanol (25%, 0.18 mL, 0.788 mmol, 1.04 equiv) was added to a solution of **17** (0.5 g, 0.758 mmol, 1.0 equiv) in methanol (3.0 mL) and stirred at room temperature. After 3 h the reaction was quenched with saturated NH_4Cl (15 mL), neutralized with HCl (3 N, three drops), and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 5:1 hexane/ethyl acetate) to afford **18** (0.273 g, 90%). TLC: R_f = 0.53 (2:1 hexane/ethyl acetate, visualization by UV, PMA). MS: $(M + NH_4)^+$ 420, $(M + H - H_2O)^+$ 385. IR: (neat) C=O 1739 cm^{-1}. $[\alpha]_D$ = +10.61° [c = 0.49, MeOH]. ^1H ($CDCl_3$): 0.73 (d, 3 H, J = 7), 0.78 (s, 3 H), 0.82 (s, 3 H), 0.90 (d, 3 H, J = 7), 1.05–1.55 (m, 5 H), 1.86–2.0 (m, 2 H), 2.5 (m, 2 H), 2.6 (d, 1 H, J = 5.3), 3.28 (dd, 1 H, J = 1.7, 9.6), 3.46 (dd, 1 H, J = 2.3, 9.6), 3.69 (s, 3 H), 4.37 (s, 3 H), 4.35–4.53 (m, 1 H), 5.3–5.5 (m, 2 H), 7.25–7.33 (m, 5 H). ^{13}C ($CDCl_3$): 15.5, 19.5, 20.2, 21.5, 26.8, 31.3, 33.1, 39.5, 41.0, 41.5, 42.6, 51.6, 51.8, 68.6, 68.7, 73.1, 127.3, 127.5, 128.1, 132.7, 132.9, 172.5. Anal. Calcd for $C_{25}H_{38}O_4$: C, 74.59; H, 9.51. Found: C, 74.52; H, 9.56.

Preparation of 19. *n*-Butyllithium (1.6 M, 10.3 mL, 16.4 mmol, 6.0 equiv) was added dropwise to a solution of diisopropylamine (2.3 mL, 16.4 mmol, 6.0 equiv) in THF (10 mL) at −78 °C. After complete addition it was stirred for an additional 15 min at −78 °C, warmed to −5 °C, and stirred for 5 min and then recooled to −78 °C. Freshly distilled *tert*-butyl acetate (2.22 mL, 16.4 mmol, 6.0 equiv) was added dropwise and the mixture stirred at −78 °C for 30 min, warmed to −25 °C for 1 h, and then recooled to −30 °C. A solution of **18** (1.1 g) in THF (7 mL) was added dropwise and stirred at −30 °C. After being stirred for 3 h, the reaction mixture was quenched sequentially with NH_4Cl (25 mL) and HCl (3 N, three drops), warmed to room temperature, and extracted with ethyl acetate (3 × 50 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 3:1 petroleum ether/diether ether) to afford **19** (0.98 g, 74%). TLC: R_f = 0.18 (3:1 petroleum ether/diethyl ether, visualization by PMA). MS: $(M + H)^+$ 489, $(M + NH_4)^+$ 506. IR: (neat, C=O 1728 cm^{-1}). $[\alpha]_D$ = +8.18 [c = 2.03, MeOH]. ^1H ($CDCl_3$): 0.73 (d, 3 H, J = 7), 0.78 (s, 3 H), 0.82 (s, 3 H), 0.90 (d, 3 H, J = 7), 1.18–1.56 (m, 5 H), 1.46 (s, 9 H), 1.9–2.0 (m, 2 H), 2.49 (d, 1 H, J = 4.1), 2.65 (m, 2 H), 3.29 (dd, 1 H, J = 1.7, 9.4), 3.45 (dd, 1 H, J = 2.3, 9.4), 3.35 (s, 2 H), 4.37 (m, 3 H), 4.45–4.55 (m, 1 H), 5.42 (m, 2 H), 7.25–7.33 (m, 5 H). ^{13}C ($CDCl_3$): 15.4, 19.4, 20.1, 21.5, 26.7, 27.9, 31.3, 33.1, 39.4, 40.9, 42.5, 49.7, 51.1, 51.7, 68.2, 68.5, 72.9, 81.9, 127.2, 127.4, 128.0, 132.3, 133.0, 138.9, 166.8, 202.9. Anal. Calcd for $C_{30}H_{46}O_5$: C, 74.04; H, 9.53. Found: C, 74.07; H, 9.91.

Preparation of 20. Triethylborane in THF (1 M, 2.4 mL, 2.4 mmol, 1.2 equiv) was stirred with 2,2-dimethylpropanoic acid

(0.012 g, 0.12 mmol, 0.06 equiv) at room temperature for 30 min. A solution of **19** (0.97 g, 2.0 mmol, 1.0 equiv) in THF (15 mL) was added and the mixture stirred for 1 h at room temperature. The solution was then cooled to −78 °C, and $NaBH_4$ (0.23 g, 6.0 mmol, 3.0 equiv) was added, followed by dropwise addition of MeOH (4.7 mL, 104 mmol, 52 equiv). After 2 h, the reaction mixture was sequentially quenched at −78 °C with H_2O_2 (30%, 5 mL, 49 mmol, 25 equiv) and H_2O (17 mL, 778 mmol, 389 equiv), warmed to room temperature and stirred for 16 h. It was then extracted with ethyl acetate (4 × 40 mL), and the combined organic extracts were dried ($MgSO_4$), filtered, and concentrated under vacuum. The residue was purified by flash chromatography (eluting with 3:1 hexane/ethyl acetate) to afford **20** (0.81 g, 83%). TLC: R_f = 0.44 (1:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + H)^+$ 489, $(M + NH_4)^+$ 506. IR: (neat) OH = 3447 cm^{-1}. $[\alpha]_D$ = +12.05 [c = 2.44, MeOH]. ^1H ($CDCl_3$): 0.73 (d, 3 H, J = 6.5), 0.78 (s, 3 H), 0.83 (s, 3 H), 0.90 (d, 3 H, J = 7), 1.1–1.7 (m, 7 H), 1.46 (s, 9 H), 1.88–2.0 (m, 2 H), 2.3–2.47 (m, 3 H), 2.79 (s, 1 H), 3.32 (dd, 1 H, J = 2.0, 9.0), 3.46 (dd, 1 H, J = 2.0, 9.0), 3.72 (d, 1 H, J = 1.8), 4.12–4.43 (m, 2 H), 4.37 (s, 2 H), 5.33–5.5 (m, 2 H), 7.25–7.35 (m, 5 H). ^{13}C ($CDCl_3$): 15.4, 19.4, 20.1, 21.4, 26.7, 27.9, 31.6, 33.1, 39.4, 40.9, 42.5, 42.6, 42.9, 51.7, 68.1, 68.7, 72.4, 73.0, 81.0, 127.1, 127.3, 128.0, 131.8, 134.6, 138.9, 171.7. Anal. Calcd for $C_{30}H_{48}O_5$: C, 73.73; H, 9.90. Found: C, 73.93; H, 10.11.

Preparation of 21. Lithium hydroxide (1 N, 0.359 mL, 0.359 mmol, 1.0 equiv) was added to a solution of **20** (0.175 g, 0.359 mmol, 1.0 equiv) in dioxane (3.5 mL) and the resulting solution stirred at room temperature. Additional amounts of 1 N lithium hydroxide (0.18 mL, 0.18 mmol, 0.5 equiv after 20 min and 2.0 mL, 5.6 equiv after 1 h) were added to ensure completion of reaction. The reaction was concentrated under vacuum and the residue chromatographed on a column of CHP-20P gel (eluting sequentially with H_2O (400 mL) and CH_3CN (33%, 200 mL)) to afford **21** (0.152 g, 96%) as the lithium salt. TLC: R_f = 0.38 (20:1:1 methylene chloride/methanol/acetic acid). MS: $(M + Li)^+$ 439, $(M - 2H + Li)^-$ 437. IR: (KBr) COO^- = 1585 cm^{-1}. $[\alpha]_D$ = +8.73° [c = 0.55, MeOH]. ^1H ($CDCl_3$): 0.71 (d, 3 H, J = 7.0), 0.75 (s, 3 H), 0.81 (s, 3 H), 0.86 (d, 3 H, J = 7), 1.1–1.54 (m, 7 H), 1.78–1.87 (m, 2 H), 1.87–1.98 (m, 1 H), 1.98–2.07 (m, 1 H), 2.5 (m, 1 H), 3.2–3.5 (m, 2 H), 3.75 (m, 1 H), 4.1 (m, 1 H), 4.26–4.4 (m, 2 H), 4.68 (br s, 1 H), 5.2–5.34 (m, 2 H), 7.24–7.35 (m, 5 H). Anal. Calcd for $C_{26}H_{39}O_5 \cdot 0.64H_2O$: C, 69.39; H, 9.02. Found: C, 69.39; H, 8.74.

Preparation of 22. pTsOH (30 mg, 0.026 mmol) was added in one portion to a solution of diol **20** (743 mg, 1.522 mmol) and 2,2-dimethoxypropane (181 μL, 2.285 mmol) in acetone (10 mL). After the mixture was stirred for 3 h at rt, Et_3N (25 μL, 0.18 mmol) was added and the reaction mixture was concentrated in vacuo. The residue was taken up in EtOAc (100 mL) and washed sequentially with H_2O (1 × 50 mL) and saturated aqueous $NaHCO_3$ (1 × 50 mL). Drying and concentration gave 840 mg of crude product which was purified by flash chromatography (19:1 hexane/EtOAc) to yield 717 mg (89.2%) of pure **22**. TLC: R_f = 0.53 (4:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + NH_4)^+$ 546. IR: (KBr) 2958, 2897, 2870, 1732, 1367, 1257, 1199, 1157. $[\alpha]_D$ = +11.36° [c = 2.5, MeOH]. ^1H ($CDCl_3$): 0.73 (d, 3 H, J = 7), 0.78 (s, 3 H), 0.83 (s, 3 H), 0.89 (d, 3 H, J = 7), 1.1–1.6 (m, 7 H), 1.38 (s, 3 H), 1.45 (s, 9 H), 1.46 (s, 3 H), 1.85–2.02 (m, 2 H), 2.28 (dd, 1 H, J = 6.3, 15.2), 2.42 (dd, 1 H, J = 7, 15.2), 3.3 (dd, 1 H, J = 1.8, 9.4), 3.45 (dd, 1 H, J = 2.3, 9.4), 4.36 (s, 2 H), 4.2–4.42 (m, 2 H), 5.28–5.45 (m, 2 H), 7.23–7.35 (m, 5 H). ^{13}C ($CDCl_3$): 15.4, 19.5, 19.6, 20.1, 21.4, 26.8, 28.0, 30.0, 31.4, 33.1, 36.9, 39.5, 40.9, 42.6, 42.7, 51.8, 65.9, 68.7, 69.4, 73.0, 80.2, 98.5, 127.1, 127.3, 128.0, 131.4, 133.0, 138.9, 170.0. Anal. Calcd for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.70; H, 10.26.

Preparation of 23. Pearlman's catalyst ($Pd(OH)_2/C$, 15 mg) was added to a solution of the benzyl ether **22** (353 mg, 0.668 mmol) in EtOAc (20 mL) and the solution stirred under a 1 atm pressure of hydrogen at rt. After 2 h, additional catalyst (10 mg) was added, and the reaction was judged to be complete by TLC after an additional 2 h. The reaction mixture was filtered through a small bed of Celite, and the catalyst was washed with additional EtOAc. The combined filtrate was concentrated in vacuo to give 294 mg (100%) pure **23**. TLC: R_f = 0.12 (4:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + Cl)^-$ 473$^-$, $(M + NH_4)^+$ 456. IR: (KBr) 3443, 2960, 2947, 2899, 2874, 1722, 1633, 1458, 1384, 1369, 1317, 1259, 1199, 1163, 1084, 1051, 1028, 981, 945, 873, 844. $[\alpha]_D$ = +4.43° [c = 1.15, MeOH]. ^1H ($CDCl_3$): 0.78 (d, 3 H, J = 7), 0.8 (s, 3 H), 0.84 (s, 3 H), 0.92 (d, 3 H, J = 7), 1.1–1.15 (m, 6 H), 1.38 (s, 3 H), 1.45 (s, 9 H), 1.47 (s, 3 H), 1.62 (dt, J = 2.3, 12.9), 1.75–1.85 (m, 1 H), 2.02–2.07 (m, 1 H), 2.30 (dd, 1 H, J = 5.9, 15.2), 2.42 (dd, 1 H, J = 6.7, 15.2), 3.55–3.7 (m, 2 H), 4.2–4.4 (m, 2 H), 5.46–5.49 (m, 2 H). ^{13}C ($CDCl_3$): 15.4, 19.5, 19.7, 20.2, 21.5, 26.9, 28.0, 30.1, 31.4, 33.2, 37.0, 40.8, 41.0, 42.0, 42.6, 52.3, 61.2, 66.1, 69.1, 80.5, 98.7, 132.0, 132.9, 170.3. Anal. Calcd for $C_{26}H_{46}O_5$: C, 71.19; H, 10.57. Found: C, 71.47; H, 10.95.

Preparation of 24. DMAP (11 mg, 0.089 mmol) and freshly distilled 2,2-dimethylbutyryl chloride (216 mg, 1.606 mmol) were sequentially added to a solution of the alcohol **23** in pyridine (5 mL), and the reaction was left to stir overnight at rt. After 15 h, the reaction mixture was partitioned between EtOAc (100 mL) and H_2O (30 mL). The organic solution was washed sequentially with H_2O (2 × 30 mL) and 10% aqueous HCl (2 × 30 mL). Drying and concentration gave the crude product which was purified by flash chromatography (19:1 hexane/EtOAc) to yield 427 mg (89.5%) of pure **24**. TLC: R_f = 0.51 (4:1 hexane/ethyl acetate, visualization by PMA). MS: $(M - H)^-$ 535, $(M + NH_4)^+$ 554. IR: (neat) 2965, 2942, 2912, 2873, 1730, 1474, 1463, 1386, 1380, 1368, 1315, 1258, 1243, 1201, 1160, 1111, 1088, 1062, 1033, 1018, 974, 950, 875, 847. $[\alpha]_D$ = +16.6° [c = 2.45, MeOH]. ^1H ($CDCl_3$): 0.76 (d, 3 H, J = 7), 0.82 (s, 3 H), 0.83 (t, 3 H, J = 7.6), 0.86 (s, 3 H), 0.88 (d, 3 H, J = 7), 1.14 (s, 6 H), 1.36 (s, 3 H), 1.44 (s, 9 H), 1.46 (s, 3 H), 1.53 (q, 2 H, J = 7.6), 1.1–1.6 (m, 6 H), 1.79–1.89 (m, 2 H), 2.28 (dd, 1 H, J = 5.9, 15.2), 2.39 (dd, 1 H, J = 7, 15.2), 3.84 (dd, 1 H, J = 2.2, 11.1), 4.17 (dd, 1 H, J = 2.2, 11.1), 4.2–4.35 (m, 2 H), 5.3–5.36 (m, 2 H). ^{13}C ($CDCl_3$): 9.3, 15.3, 19.5, 19.6, 20.0, 21.2, 24.6, 24.8, 26.8, 28.0, 30.0, 31.5, 33.2, 33.3, 37.1, 38.1, 41.1, 42.6, 42.8, 42.9, 52.3, 62.4, 65.9, 69.6, 80.3, 98.5, 130.8, 133.9, 170.1, 177.6. Anal. Calcd for $C_{32}H_{56}O_6$: C, 70.42; H, 10.53. Found: C, 70.60; H, 10.35.

Preparation of 25. pTsOH (15 mg, 0.013 mmol) was added in one portion to a solution of the acetonide **24** (194 mg, 0.362 mmol) in 2.5% aqueous MeOH (10 mL), and the reaction was judged to be complete by TLC after being stirred for 1 h at rt. Et_3N (20 μL, 0.144 mmol) was added, and the reaction mixture was concentrated under vacuo. The crude product was purified by flash chromatography (4:1–2:1 hexane/EtOAc) to yield 173 mg (96.3%) of pure **25**. TLC: R_f = 0.46 (1:1 hexane/ethyl acetate, visualization by PMA). IR: (neat) 3445, 2963, 2934, 2905, 2872, 1727, 1473, 1388, 1367, 1253, 1158. $[\alpha]_D$ = +21.9° [c = 0.96, MeOH]. ^1H ($CDCl_3$): 0.76 (d, 3 H, J = 6.5), 0.82 (s, 3 H), 0.83 (t, 3 H, J = 7.6), 0.86 (s, 3 H), 0.89 (d, 3 H, J = 6.5), 1.13 (s, 3 H), 1.14 (s, 3 H), 1.46 (s, 9 H), 1.57 (q, 2 H, J = 7.6), 1.1–1.7 (m, 6 H), 1.75–1.95 (m, 2 H), 2.37 (d, 2 H, J = 5.3), 3.1 (d, 1 H, J = 1.7), 3.78 (d, 1 H, J = 2.35), 3.91 (dd, 1 H, J = 1.7, 11.7), 4.15 (dd, 1 H, J = 2.0, 11.7), 4.17–4.21 (m, 1 H), 4.34–4.38 (m, 1 H), 5.32–5.48 (m, 2 H). ^{13}C ($CDCl_3$): 9.3, 15.3, 19.5, 20.0, 21.2, 24.6, 24.8, 26.8, 28.0, 31.4, 33.1, 33.3, 38.2, 41.1, 42.6, 42.8, 42.9, 43.0, 52.3, 62.6, 68.3, 72.5, 81.1, 131.0, 135.5, 171.8, 177.8. Anal. Calcd for $C_{29}H_{52}O_6$: C, 70.12; H, 10.55. Found: C, 70.04; H, 10.54.

Preparation of 26. 5% Rh/Al_2O_3 (30 mg) was added to a solution of the olefin **25** (98 mg, 0.197 mmol) in EtOAc (9 mL) and the solution stirred under hydrogen (balloon) at rt. After 3 h, the reaction was judged to be complete by TLC. The reaction mixture was filtered through a small bed of Celite, and the catalyst was washed with additional EtOAc. The combined filtrate was concentrated in vacuo, and the crude product was purified by flash chromatography (4:1–2:1 hexane/EtOAc) to give 83 mg (84.3%) of pure **26**. TLC: R_f = 0.25 (2:1 hexane/ethyl acetate, visualization by PMA). MS: $(M + H)^+$ 499, $(M + NH_4)^+$ 516. IR: (neat) 3439, 2962, 2933, 2881, 1727, 1472, 1459, 1389, 1367, 1156. $[\alpha]_D$ = +4.4° [c = 0.91, MeOH]. ^1H ($CDCl_3$): 0.75 (d, 3 H, J = 6.5), 0.77 (s, 3 H), 0.84 (t, 3 H, J = 7.0), 0.87 (d, 3 H, J = 6.5), 0.93 (s, 3 H), 1.46 (s, 9 H), 0.98–1.92 (m, 14 H), 2.37 (d, 2 H, J = 6.45), 3.42 (s, 1 H), 3.8 (m, 2 H), 3.99 (d, 1 H, J = 11.7), 4.2 (m, 1 H), 4.28 (d, 1 H, J = 11.7). ^{13}C ($CDCl_3$): 9.3, 15.3, 19.4, 19.6, 21.4, 24.5, 24.8, 25.5, 26.6, 28.0, 30.8, 33.2, 34.3, 39.8, 40.7, 41.6, 42.2, 42.7, 42.9, 43.7, 47.4, 61.9, 69.1, 72.5, 81.3, 171.9, 178.1. Anal. Calcd for $C_{29}H_{54}O_6$: C, 69.84; H, 10.91. Found: C, 69.87; H, 11.38.

Preparation of 3a. 1 N LiOH (250 μL, 0.25 mmol) was added to a solution of the ester **26** (113 mg, 0.227 mmol) in freshly distilled dioxane (5 mL). After 0.5 h, additional 1 N LiOH (50 μL, 0.05 mmol) was added, and the reaction was judged to be

complete by TLC after being stirred for an additional 1.5 h. The reaction mixture was concentrated in vacuo and the residue purified by CHP 20 (3:1 H_2O/MeCN). The appropriate fractions were combined and concentrated to remove MeCN. The remaining aqueous solution was millipore filtered and lyophilized to afford 92 mg (89%) of pure **3a** as its lithium salt. TLC: R_f = 0.28 (20:1:1 CH_2Cl_2/MeOH/AcOH, visualization by PMA). Mp = 186–188 °C. MS: $(M - H)^-$ 441, $(M + Li)^+$ 449. IR: (KBr) 3432, 2934, 2879, 1724, 1583, 1391, 1248, 1165. $[\alpha]_D$ = +1.4° [c = 0.5, MeOH]. ^1H (CD_3OD): 0.79 (d, 3 H, J = 7.6), 0.80 (s, 3 H), 0.85 (t, 3 H, J = 7.0), 0.86 (d, 3 H, J = 7.6), 0.95 (s, 3 H), 1.14 (s, 3 H), 1.16 (s, 3 H), 1.0–1.95 (m, 14 H), 2.24 (dd, 1 H, J = 7.9, 15.2), 2.35 (dd, 1 H, J = 4.7, 15.2), 3.7 (quint, 1 H), 4.0 (d, 1 H, J = 11.7), 4.08 (quint, 1 H), 4.36 (dd, 1 H, J = 1.7, 11.7). Anal. Calcd for $C_{25}H_{45}LiO_6 \cdot 0.7\ H_2O$: C, 65.11; H, 10.14. Found: C, 65.07; H, 10.40.

Preparation of 3b. 1 N LiOH (250 μL, 0.25 mmol) was added to a solution of the ester **25** (110 mg, 0.222 mmol) in freshly distilled dioxane (5 mL). After 2 h, additional 1 N LiOH (100 μL, 0.1 mmol) was added, and the reaction was judged to be complete by TLC after being stirred for an additional 1 h. The reaction mixture was concentrated in vacuo and the residue purified by CHP 20 (3:1 H_2O/MeCN). The appropriate fractions were combined and concentrated to remove MeCN. The remaining aqueous solution was millipore filtered and lyophilized to afford 85 mg (84.5%) of pure **3b** as its lithium salt. TLC: R_f = 0.24 (20:1:1 CH_2Cl_2/MeOH/AcOH, visualization by PMA). Mp = 168–178 °C. MS: $(M + Li)^+$ 447. IR: (KBr) 3420, 2961, 1725, 1585, 1422, 1250, 1164. $[\alpha]_D$ = +21.1° [c = 0.5, MeOH]. ^1H (CD_3OD): 0.8 (d, 3 H, J = 7), 0.85 (t, 3 H, J = 7.0), 0.86 (s, 3 H), 0.89 (s, 3 H), 0.92 (d, 3 H, J = 7), 1.14 (s, 3 H), 1.15 (s, 3 H), 1.1–1.4 (m, 3 H), 1.45–1.65 (m, 6 H), 1.66–1.74 (m, 1 H), 1.85–1.90 (m, 2 H), 2.23 (dd, 1 H, J = 7.7, 15.4), 2.38 (dd, 1 H, J = 4.4, 15.4), 3.93 (dd, 1 H, J = 2.2, 11.7), 4.02 (m, 1 H), 4.22 (dd, 1 H, J = 2.2, 11.7), 4.26–4.29 (m, 1 H), 5.37–5.48 (m, 2 H). Anal. Calcd for $C_{25}H_{43}LiO_6 \cdot 0.5H_2O$: C, 65.92; H, 9.73. Found: C, 66.14; H, 9.86.

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Registry No. **3a**·Li, 144225-27-4; **3b**·Li, 144225-28-5; **4**, 69153-92-0; **5**, 144225-29-6; **6**, 144225-30-9; **7**, 144225-31-0; **8** (isomer 1), 144225-32-1; **8** (isomer 2), 144300-60-7; **8** (isomer 3), 144300-61-8; **8** (isomer 4), 144300-62-9; (*E*)-**9**, 144225-33-2; (*Z*)-**9**, 144300-63-0; **10a**, 144225-34-3; **10b**, 144300-64-1; **11**, 96555-58-7; **13**, 144225-35-4; **14a** (isomer 1), 144225-36-5; **14a** (isomer 2), 144300-65-2; **14b** (isomer 1), 144225-37-6; **14b** (isomer 2), 144300-66-3; **14b** (isomer 3), 144300-67-4; **14b** (isomer 4), 144300-68-5; **15**, 119673-72-2; **17**, 144225-38-7; **18**, 144225-39-8; **19**, 144225-40-1; **20**, 144225-41-2; **21**·Li, 144225-42-3; **22**, 144225-43-4; **23**, 144225-44-5; **24**, 144225-45-6; **25**, 144225-46-7; **26**, 144225-47-8; **27**, 6553-64-6; **28**, 144225-48-9; **30**, 144225-49-0; **31**, 144225-50-3; **32** (isomer 1), 144225-51-4; **32** (isomer 2), 144300-69-6; **33** (isomer 1), 144225-52-5; **33** (isomer 2), 144300-70-9; **34** (isomer 1), 144225-53-6; **34** (isomer 2), 144300-71-0; **35**, 144225-54-7; **36** (isomer 1), 144225-55-8; **36** (isomer 2), 144300-72-1; (*S*)-HYTRA, 95061-51-1; (*R*)-(−)-carvone, 6485-40-1; HMT-CoA reductase, 9028-35-7; cholesterol, 57-88-5.

Zaragozic Acid A, a Potent Inhibitor of Squalene Synthase: Initial Chemistry and Absolute Stereochemistry

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Chemical studies on the highly potent squalene synthase inhibitor zaragozic acid A (1) have led to the determination of the total absolute stereochemistry of the molecule as shown in Figure 3 and to the feasibility of selectively manipulating the carboxyl and ester groups of the molecule. The absolute stereochemistry of the central core of 1 was established based on CD measurements on the bis(4-bromobenzoate) 8. The configuration of the methyl group in the C1 alkyl side chain was deduced by degrading 1 to (*R*)-(−)-2-methyl-3-phenylpropanoic acid, while the configuration of the adjacent acetoxy group was established from ^1H NMR considerations of the (*R*)- and (*S*)-*O*-methyl mandelates **14** and **15**. Single-crystal X-ray diffraction data on two crystalline derivatives (**16** and **17**) not only led to clarification of the asymmetric centers in the 4,6-dimethyl-2-octenoyl side chain but also afforded independent structural confirmation of the nature of the chemical and biological heart of zaragozic acid A.

Introduction

The screening of fermentation cultures for natural products that inhibit specific enzymatic steps in the synthesis of cholesterol has proven to be remarkably productive. Most significant were the codiscoveries of ML-236B and compactin from fermentations of *Penicillium* spp. and of monacolin K and mevinolin from fermentations of *Monascus ruber* and *Aspergillus terreus*, respectively.[1] These compounds and derivatives thereof are all potent inhibitors of the enzyme HMG-CoA reductase and have established themselves clinically as highly effective agents to reduce serum cholesterol in man. In addition to inhibitors of the reductase enzyme, screening activities by various research groups have resulted in the discovery of potent inhibitors to two earlier enzymes in the pathway from acetate to cholesterol, namely acetoacetyl-CoA thiolase[2] and HMG-CoA synthase.[3]

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