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DIASTEREO- AND ENANTIOSELECTIVE PREPARATION OF β-ALKYLHOMOALLYLIC ALCOHOLS

SYNTHESIS OF SERRICORNIN AND CORYNOMYCOLIC ACID

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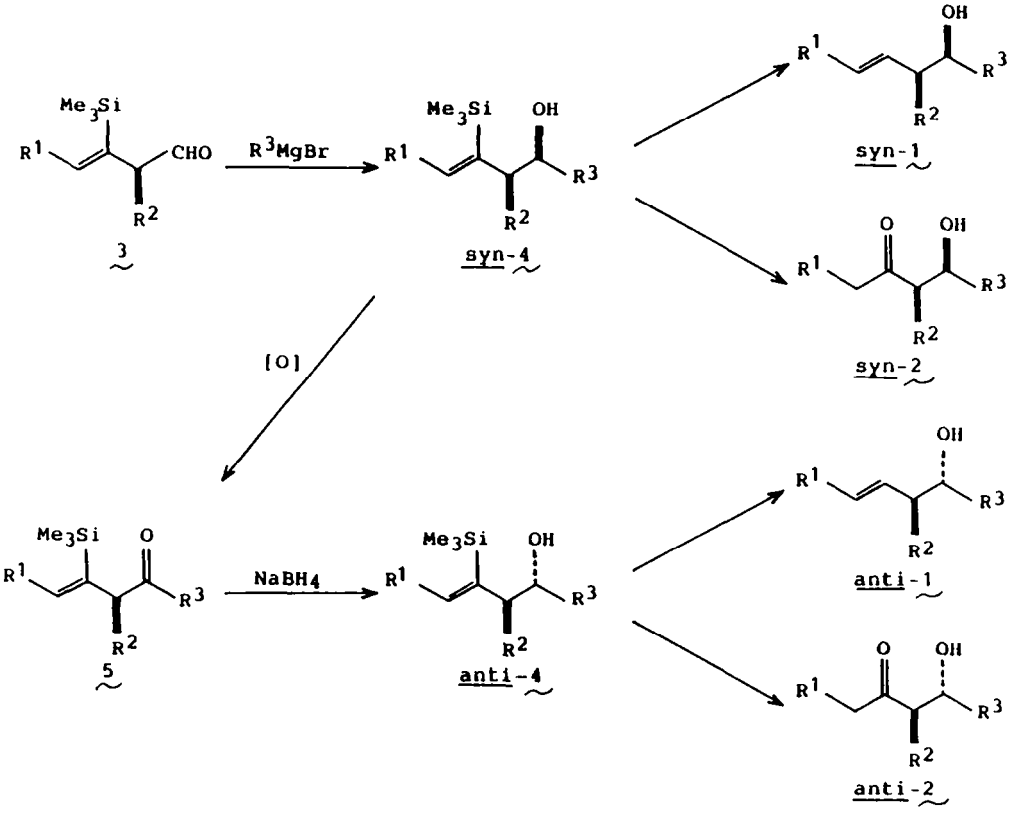
Abstract—A new and efficient method for the preparation of four possible stereoisomers of β-alkylhomoallylic alcohols **1** has been developed which is based on the diastereoselective addition of nucleophiles to optically active α-alkyl-β-trimethylsilyl-β,γ-unsaturated carbonyl compounds. The utility of this reaction is demonstrated by the synthesis of naturally occurring serricornin and corynomycolic acid.

The diastereo- and enantioselective preparation of β-alkylhomoallylic alcohols **1** and β-hydroxy-α-alkyl ketones **2** has attracted much interest in relation to the synthesis of natural products such as macrolide and ionophore antibiotics.[1] Alcohols **1** have been prepared by steroselective addition of allylic metal compounds to aldehydes[2] or via sigmatropic rearrangements,[3] and ketones **2** have been prepared effectively by stereoregulated aldol condensations.[4]

Recently we have developed[5,6] a new and efficient method for the preparation of **1** and **2** which is based on the diastereoselective addition of nucleophiles to chiral carbonyl compounds (Scheme 1). Thus, the aldehydes **3** react with Grignard reagents with high diastereoselectivity affording the *syn*-alcohols **4** ("Cram" products),[7] and the *syn*-products **4** are selectively converted into their diastereoisomers, *anti*-**4** ("Cram" products), via oxidation to the ketones **5** followed by reduction with $NaBH_4$. The products **4** thus obtained can be readily converted to **1** and **2** by use of the reactivities of the vinylsilyl moiety.[8]

The high selectivity observed in this nucleophilic



Scheme 1.

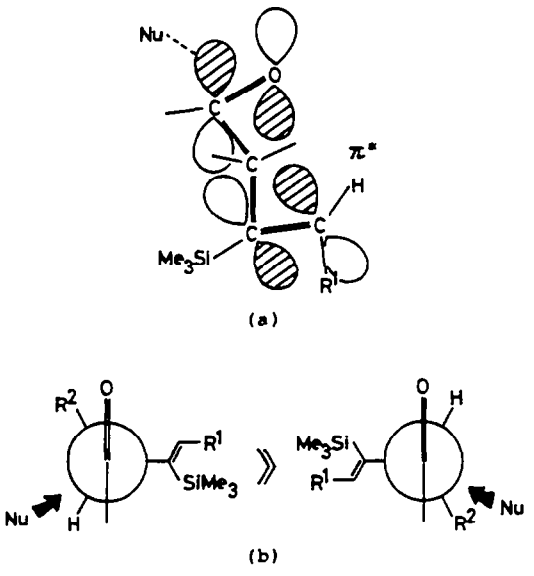


Fig. 1. (a) Stereo view of the supermolecule including π^* orbitals. (b) Direction of nucleophilic attack.

addition reaction can be explained by the Felkin–Anh model.[9] Thus, the supermolecule [nucleophile (Nu) + carbonyl compound] shown in Fig. 1 is the most stable when the vinyl group is perpendicular to the carbonyl plane resulting in a $\pi^*_{C=O}$–$\pi^*_{C=C}$ interaction, and nucleophilic attack occurs from the less-hindered side to avoid steric interactions.[10]

Herein we report a general synthetic method for the preparation of the chiral aldehyde (*R*)- and (*S*)-**3** and the preparation of all possible stereoisomers of homoallylic alcohols **1** and **4** according to Scheme 1.[11a,12] The utility of the present reaction is demonstrated by the stereoselective synthesis of serricornin[11b] and corynomycolic acid.[11c]

RESULTS AND DISCUSSION

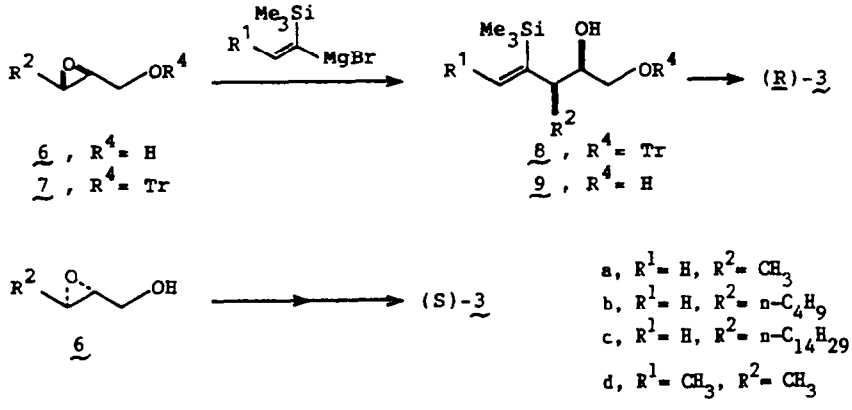
Preparation of the optically active aldehyde **3**

The optically active aldehyde (*R*)-**3** was synthesized as shown in Scheme 2 starting with the optically active (2*S*,3*S*)-epoxide **6** (>95% e.e.), which was readily prepared by Katsuki and Sharpless asymmetric epoxidation of the corresponding (*E*)-alk-2-en-1-ol using (+)-dialkyl tartrate.[13] After protection of **6** as a trityl ether,[14] **7** was treated with 1-trimethylsilyl-1-alkenylmagnesium bromide in the presence of a catalytic amount of CuI to give **8** as the sole product.[15] Deprotection of crude **8** in aqueous $CHCl_2COOH$ gave **9**, which was finally converted to (*R*)-**3** by treatment with $NaIO_4$. The aldehyde (*S*)-**3** was synthesized using the same method starting from (2*R*,3*R*)-**6**, which was obtained by the epoxidation of (*E*)-alk-2-en-1-ol using (−)-dialkyl tartrate.[13] Thus, **3a** was prepared from **6a**[13b] and CH_2=C($SiMe_3$)MgBr, **3b** from **6b** and CH_2=C($SiMe_3$)MgBr, **3c** from **6c** and CH_2=C($SiMe_3$)MgBr, and **3d** from **6d** and (*Z*)-MeCH=C($SiMe_3$)MgBr prepared by hydromagnesiation[16] of 1-trimethylsilyl-1-propyne. The enantiomeric purity of **3** thus prepared was confirmed to be >95% by ^{1}H-NMR spectroscopy using the chiral shift reagent (+)-tris[di(perfluoro-2-propoxypropionyl)-methanate]praseodymium(III) [(+)-Pr(DPPM)$_3$].[17] The specific rotations and yields of **3** are summarized in Table 1.

Since both enantiomers of **6**[13] and various Grignard reagents of general formula CH(R^1)=C($SiMe_3$)-MgBr[16] can be readily prepared, the present procedure provides a practical and general method for the synthesis of a wide variety of the optically active aldehydes **3**.

Synthesis of four possible stereoisomers of the homoallylic alcohols **1** *and* **4**

Since we succeeded in preparing the chiral aldehydes **3**, it is feasible to synthesize the optically active β-alkylhomoallylic alcohols **1** and **4** and the α-alkyl-β-hydroxy carbonyl compounds **2** according to Scheme 1.[5] To confirm the enantiomeric integrity of the products during the transformations shown in Scheme 1, we carried out the synthesis of the four possible stereoisomers of **1a** (R^3 = Et) and **4a** (R^3 = Et) from **3a** and EtMgBr. The specific rotations of the products **1a** (R^3 = Et) and **4a** (R^3 = Et), which are summarized in Table 2, indicate that each product has a high optical purity. We confirmed this point by converting *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) and *anti*-(3*S*,4*R*)-**1a** (R^3 = Et) to the known compounds **11**[18] and **15**,[19] respectively



Scheme 2.

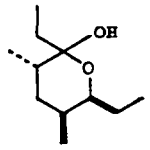
Table 1. Specific rotations and overall yields of **3** from **6**

Compound	R^1	R^2	Configuration	$[\alpha]_D^{25}$ (*c* in $CHCl_3$)	Yield (%)
3a	H	CH_3	*R*	+77.0° (1.04)	67
3a	H	CH_3	*S*	−75.6° (0.516)	67
3b	H	n-C_4H_9	*R*	−16.7° (1.04)	68
3c	H	n-$C_{14}H_{29}$	*R*	−13.3° (0.900)	47
3d	CH_3	CH_3	*R*	+126° (1.04)	53

(Scheme 3). Protection of *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) as a triethylsilyl ether followed by ozonolysis afforded the aldehyde **11** in 93% yield. On the other hand, **15** was prepared as follows. Ozonolysis of the benzyl ether of *anti*-(3*S*,4*R*)-**1a** (R^3 = Et) followed by Jones oxidation, esterification with CH_2N_2 and deprotection afforded compound **15**. The optical purities of **11** and **15** thus prepared were found to be *ca* 95% e.e. by comparison of the rotation values in the literature.[18,19]

Synthesis of (4*S*,6*S*,7*S*)-*serricornin* (**16**)

Serricornin (**16**) is the sex pheromone of the cigarette bettle (*Lasioderma serricone* F), which is a major pest of cured tobacco leaves.[20] Recently, the absolute stereochemistry of serricornin (**16**) was established by Mori *et al.* as 4*S*,6*S*,7*S* for its open-chain acetate **17**.[21] Because of the practical value of serricornin, its synthesis has attracted much attention.[20b,21,22] We synthesized serricornin according to Scheme 4 starting with the optically active *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) prepared as described above.



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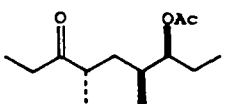

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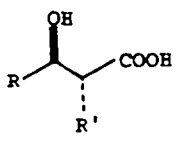
Hydromagnesiation[23] of *syn*-(3*S*,4*S*)-**1a** (R^2 = Et) with i-BuMgCl in the presence of a catalytic amount of Cp_2TiCl_2 (10 mol%) in THF followed by treatment with gaseous CO_2 and addition of formic acid to the reaction mixture afforded the lactone **19** in 54% overall yield. It should be noted here that lactone **19** has also been synthesized via hydroformylation of *syn*-**1a** (R^3 = Et) and subsequent oxidation of the resulting cyclic hemiacetal, as recently reported by Wuts *et al.*[24] Methylation of the lactone enolate derived from **19** proceeded diastereoselectively,[25] affording the lactone **20** exclusively in 86% yield. Reaction of **20** with EtMgBr afforded (4*S*,6*S*,7*S*)-serricornin (**16**). The product **16** was converted into its acetate **17** [$[\alpha]_D^{23}$ −17.9° (*c* 0.168, hexane); Ref. 21*b*: −17.7° (*c* 0.155)] in 68% yield from **20**. The ^{1}H- and ^{13}C-NMR spectral data of **17** were in accord with the values reported in the literature.[21b]

A general synthetic method for the preparation of mycolic acids

Mycolic acids, mostly found in nature as esters of carbohydrates, are high-molecular-weight fatty acids having 28–90 carbon atoms and have the basic structure RCH(OH)CH(R')COOH.[26] The stereochemistry of mycolic acids examined so far have been shown to be 2*R*,3*R*, as illustrated in formula **21**.[27]



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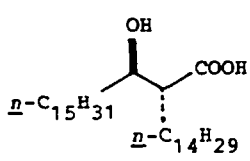

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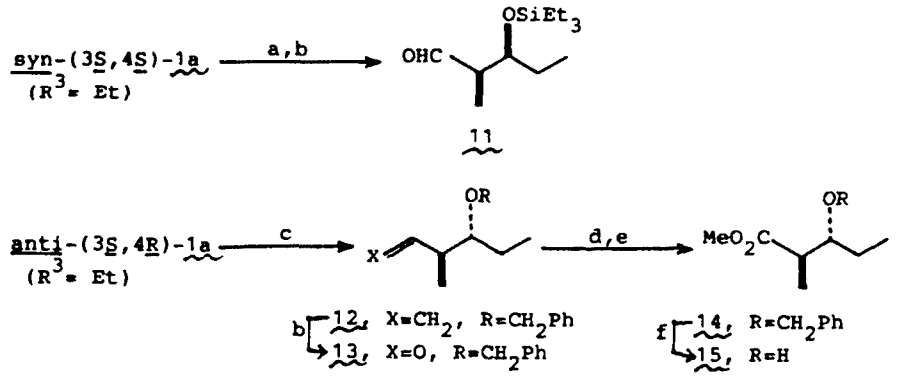
Although these acids have interesting biological properties,[26] only a few syntheses of racemic forms of **21** have been reported where the 2,3-*anti* stereochemistry was achieved with rather low stereoselectivities.[28] Furthermore, these methods do not seem to be applicable to the synthesis of enantiomerically pure **21**. To demonstrate the effectiveness of our new method for the preparation of the optically active β-alkylhomoallylic alcohols **1**, we next chose **21** as a

Table 2. Absolute configuration and specific rotation of **1a** (R^3 = Et) and **4a** (R^3 = Et) prepared by the procedure shown in Scheme 1

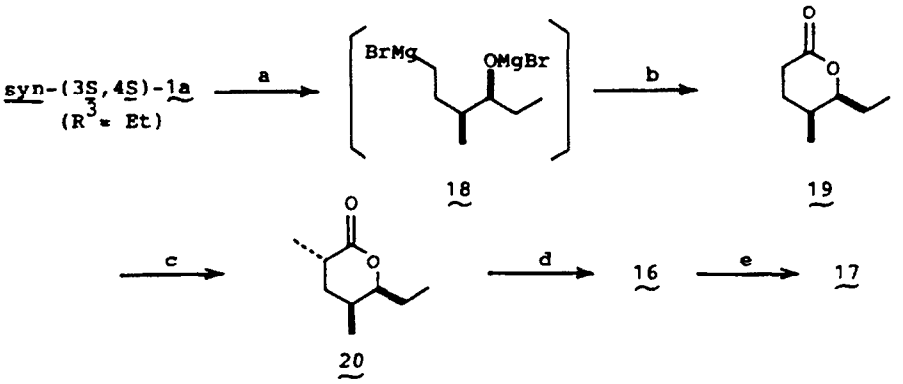
4a (R^3 = Et)[a]		**1a** (R^3 = Et)[a]	
Configuration	$[\alpha]_D^{25}$ (*c* in $CHCl_3$)	Configuration	$[\alpha]_D^{25}$ (*c* in $CHCl_3$)
(3*R*,4*S*)	−26.9° (1.04)[b]	(3*S*,4*S*)	−45.0° (0.952)[b]
(3*R*,4*R*)	−13.9° (1.41)[b]	(3*S*,4*R*)	−12.2° (0.426)[b]
(3*S*,4*R*)	+26.2° (1.00)	(3*R*,4*R*)	+45.0° (0.600)
(3*S*,4*S*)	+14.0° (0.998)	(3*R*,4*S*)	+12.5° (0.880)

[a] Diastereoisomeric purities were >99%.

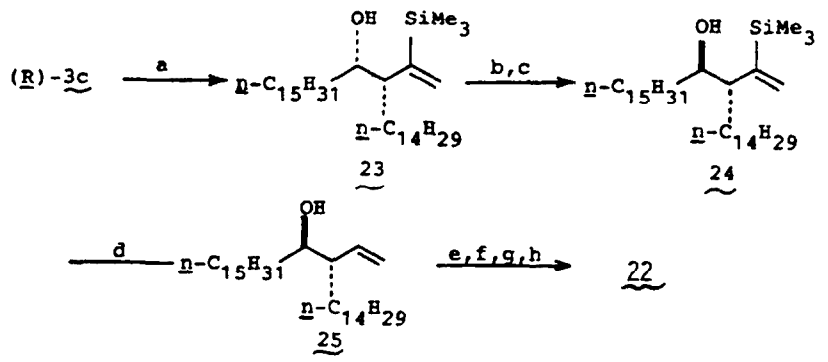
[b] Optical purities (*ca* 95% e.e.) were determined by converting them to the known compounds **11** and **15**. See text.



Scheme 3. (a) Et_3SiCl, DMAP, Et_3N; (b) O_3 then Me_2S; (c) $PhCH_2Br$, KH, THF; (d) CrO_3–H_2SO_4; (e) CH_2N_2; (f) H_2, Pd/C, EtOH.



Scheme 4. (a) i-BuMgCl, Cp_2TiCl_2 (cat), THF; (b) CO_2 (gas) then HCOOH; (c) MeI, $LiN(SiMe_3)_2$; (d) EtMgBr, THF; (e) Ac_2O, C_5H_5N.



Scheme 5. (a) n-$C_{15}H_{31}MgBr$, Et_2O, −78°; (b) CrO_3–H_2SO_4; (c) L-Selectride, THF, −45°; (d) NaH, THF–HMPA (1:3); (e) $PhCH_2Br$, KH; (f) O_3 then Me_2S; (g) CrO_3–H_2SO_4; (h) H_2, Pd/C, AcOEt.

target molecule, and prepared (+)-corynomycolic acid **22**, one of the mycolic acids produced by *Corynebacteria*[27,29] starting from the chiral (*R*)-aldehyde **3c** (Scheme 5).

Addition of n-$C_{15}H_{31}MgBr$ to **3c** gave **23** exclusively in 90% yield. Jones oxidation of **23** followed by reduction with L-Selectride afforded **24** (84%) as the sole product. (Reduction with $NaBH_4$ in MeOH did not proceed cleanly because of the low solubility of **23** in MeOH.) Finally, **24** was transformed into **22** in excellent yield. The specific rotation [$[\alpha]_D^{25}$ +7.34° (*c* 1.90 $CHCl_3$)] and melting point (70–71.5°) of **22** thus prepared were in good agreement with the values reported by Diara and Pudles [$[\alpha]_D$ +7.5° (*c* 1.64, $CHCl_3$); m.p. 70.0°].[29a]

In this synthesis, two alkyl chains, R and R′, are incorporated individually at different stages. Thus, the present method provides a general entry to the mycolic acids.

CONCLUSIONS

Synthesis of both (*R*)- and (*S*)-2-alkyl-3-trimethylsilylalk-3-enals have been carried out by using the regiospecific ring-opening reaction of the trityl ethers of 2,3-epoxy-1-alkanols with 1-trimethylsilyl-1-alkenylmagnesium bromides as the key step. All four possible stereoisomers of β-alkylhomoallylic alcohols **1** and **4** can be prepared starting with **3** according to Scheme 1. The utility of the present methodology for the synthesis of acyclic natural products has been demonstrated by the synthesis of sericornin and corynomycolic acid.

EXPERIMENTAL

The trityl ether **7a**. A mixture of the epoxy alcohol (2*S*,3*S*)-**6a**[13b] (4.8 g, 54.4 mmol, >95% e.e.), NEt_3 (23 ml, 160 mmol), TrCl (19 g, 65 mmol) and DMAP (250 mg, 2 mmol) in CH_2Cl_2 (40 ml) was stirred at 30° for 3 h and diluted with Et_2O (10 ml). The resulting mixture was passed through a pad of Celite to remove $NEt_3 \cdot HCl$. The filtrate was washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by chromatography on silica gel to give **7a** (16 g, 89%): ^{1}H-NMR (CCl_4) δ 1.32 (d, J = 4.5 Hz, 3H), 2.60–2.91 (m, 2H), 3.09–3.34 (m, 2H), 7.16–7.60 (m, 15H).

Diol **9a**. To an ice-cooled soln of CuI (230 mg, 1.2 mmol) and Me_2S (0.70 ml, 9.6 mmol) in THF (20 ml) was added a soln of CH_2=C(SiMe$_3$)MgBr in THF (18 ml, 0.61 M, 11 mmol). After 30 min, a soln of **7a** (1.98 g, 6.00 mmol) in THF (15 ml) was added at 0°. Stirring was continued for 12 h at 0°. The soln was poured into sat NH_4Cl. Extraction with Et_2O followed by evaporation afforded **8a**, which was used for the next reaction without purification.

Alcohol **8a** in 60% aq $CHCl_2COOH$ (15 ml) was stirred vigorously at room temp for 1 h and the resulting mixture was neutralized with 10% NaOH at 0°. Extraction with CH_2Cl_2 followed by chromatography on silica gel afforded **9a** (950 mg, 84% from **7a**): ^{1}H-NMR (CCl_4) δ 0.02 (s, 9H), 0.97 (d, J = 8 Hz, 3H), 2.20 (quint, J = 8 Hz, 1H), 3.05–3.70 (m, 3H), 4.04–4.26 (br s, 2H), 5.41 and 5.65 (2d, J = 3 Hz, 2H); $[\alpha]_D^{25}$ −12.4° (*c* 1.29, $CHCl_3$).

Preparation of (*R*)-**3a**. To a soln of **9a** (310 mg, 1.65 mmol) in EtOH (5 ml) was added $NaIO_4$ (12 ml, 0.3 M in H_2O, 3.6 mmol) at 0°. After 1 h, H_2O (18 ml) was added to the white mixture. Extraction with pentane followed by chromatography on silica gel afforded (*R*)-**3a** (R^1 = H) (231 mg, 90%): ^{1}H-NMR (CCl_4) δ 0.10 (s, 9H), 1.15 (d, J = 7 Hz, 3H), 3.10 (dq, J = 2, 7 Hz, 1H), 5.57 (s, 2H), 9.31 (d, J = 2 Hz, 1H); $[\alpha]_D^{25}$ +77.0° (*c* 1.04, $CHCl_3$).

Preparation of (*R*)-**3b**. The epoxy alcohol (2*S*,3*S*)-**6b** (>95% e.e.) was prepared from (*E*)-oct-2-en-1-ol according to the literature procedure:[13] ^{1}H-NMR (CCl_4 + D_2O) δ 0.92 (t, J = 6 Hz, 3H), 1.1–1.7 (m, 6H), 2.70–2.90 (m, 2H), 3.45 (dd, J = 5, 14 Hz, 1H), 3.70 (dd, J = 2.5, 12 Hz, 1H); $[\alpha]_D^{25}$ −49.9° (*c* 1.10, PhH).

A soln of (2*S*,3*S*)-**6b** (2.0 g, 15 mmol), TrCl (5.1 g, 18 mmol), DMAP (100 mg, 0.8 mmol) and NEt_3 (6.4 ml, 45 mmol) in CH_2Cl_2 (25 ml) was stirred at 30° for 3 h. Usual workup gave **7b**, which was used for the next reaction without purification.

To a soln of CuI (0.48 g, 2.5 mmol) and Me_2S (1 ml, 13 mmol) in THF (2 ml) were added CH_2=C(SiMe$_3$)MgBr (46 ml, 25 mmol, 0.55 M in THF) and **7b** in THF (20 ml). Stirring was continued for 12 h at 0°. Usual workup followed by chromatography on silica gel gave **8b**, which was used for the next reaction without purification.

A soln of **8b** obtained above in 50% aq $CHCl_2COOH$ (10 ml) was stirred vigorously at room temp for 1 h. Usual workup followed by chromatography on silica gel gave **9b**, which was used for the next reaction without purification.

To an ice-cooled soln of **9b** obtained above in EtOH (20 ml) was slowly added $NaIO_4$ (100 ml, 0.2 M in H_2O, 20 mmol). After stirring for 1 h, H_2O was added. Usual workup followed by chromatography on silica gel afforded (*R*)-**3b** (1.7 g, 68% from **6b**): ^{1}H-NMR (CCl_4) δ 0.06 (s, 9H), 0.86 (t, J = 5.5 Hz, 3H), 1.05–2.00 (m, 6H), 2.95 (dt, J = 2.5, 6.0 Hz, 1H), 5.56 (s, 2H), 9.24 (d, J = 2.5 Hz, 1H); $[\alpha]_D^{25}$ −16.7° (*c* 1.04, $CHCl_3$).

Preparation of (*R*)-**3c**. The aldehyde (*R*)-**3c** was prepared from (2*S*,3*S*)-**6c** (>95% e.e.) as described for the preparation of (*R*)-**3b**. The spectroscopic data and the specific rotations of the intermediates are as follows. **6c**: m.p. 74.5–75.0° (recrystallized from hexane); ^{1}H-NMR ($CDCl_3$) δ 0.73–1.06 (m, 3H), 1.07–1.70 (m), 2.30–2.46 (br s, 1H), 2.80–3.01 (m, 2H), 3.53 (dd, J = 12.2, 4.3 Hz, 1H), 3.84 (dd, J = 12.2, 2.9 Hz, 1H); $[\alpha]_D^{25}$ −27.0° (*c* 0.869, $CHCl_3$). (*R*)-**3c**: ^{1}H-NMR (CCl_4) δ 0.07 (s, 9H), 0.75–1.96 (m), 2.82–3.09 (m, 1), 5.59 (s, 2), 9.25 (d, J = 2.8 Hz, 1H); $[\alpha]_D^{25}$ −13.3° (*c* 0.900, $CHCl_3$).

Preparation of (*R*)-**3d**. To a soln of i-BuMgBr (60 mmol) in Et_2O (55 ml) was added Cp_2TiCl_2 (1 g, 4 mmol) at 0° under Ar. After 10 min, 1-trimethylsilyl-1-propyne (10 ml, 72 mmol) was added. The soln was stirred at 25° for 7 h and then cooled to −50°. To this soln, a soln of CuI (1.2 g, 6.0 mmol) and Me_2S (1.5 ml, 18 mmol) in THF (2 ml) and a soln of **7d** (5.0 g, 15 mmol) in THF (20 ml) were added at −50°. The resulting soln was allowed to warm up to 0° over 2 h and stirred at 0° for 12 h. Usual workup afforded **8d**, which was converted into (*R*)-**3d** as described for the preparation of **3b**.

(*R*)-**3d**: ^{1}H-NMR (CCl_4) δ 0.16 (s, 9H), 1.10 (d, J = 7.1 Hz, 3H), 1.81 (d, J = 7.3 Hz, 3H), 3.04 (m, 1H), 6.04 (q, J = 7.3 Hz, 1H), 9.43 (d, J = 1.3 Hz, 1H); $[\alpha]_D^{25}$ +126° (*c* 1.04, $CHCl_3$).

Addition reaction of EtMgBr *to* (*R*)-**3a**: *preparation of* syn-(3*R*,4*S*)-**4a** (R^3 = Et). To a soln of (*R*)-**3a** (307 mg, 1.97 mmol) in Et_2O (10 ml) was added a soln of EtMgBr (5.9 mmol) in Et_2O (3.4 ml) at −78°. After 3 h at −78°, 3 N HCl was added. Extraction with Et_2O followed by filtration through a column of silica gel gave *syn*-(3*R*,4*S*)-**4a** (R^3 = Et) (338 mg, 92%): ^{1}H-NMR (CCl_4) δ 0.07 (s, 9H), 0.91 (t, J = 6 Hz, 3H), 0.97 (d, J = 6 Hz, 3H), 1.15–1.70 (m, 2H), 1.83 (br s, 1H), 2.30 (quint, J = 6 Hz, 1H), 3.30 (dt, J = 7, 5.5 Hz, 1H), 5.39 and 5.57 (2d, J = 3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ −1.1, 10.6, 14.2, 27.7, 43.1, 74.8, 124.7, 155.9; $[\alpha]_D^{25}$ −26.9° (*c* 1.04, $CHCl_3$).

Preparation of (*R*)-**5a** (R^3 = Et). A mixture of *syn*-(3*R*,4*S*)-**4a** (R^3 = Et) (224 mg, 1.20 mmol) and PCC (500 mg, 2.4 mmol) in CH_2Cl_2 (5 ml) was stirred vigorously at room temp for 3 h. A mixture of hexane and Et_2O (5:1) (5 ml) was added to the reaction mixture. Usual workup followed by chromatography on silica gel afforded (*R*)-**5a** (R^3 = Et) (215 mg, 97%): ^{1}H-NMR (CCl_4) δ 0.12 (s, 9H), 0.92 (t, J = 7 Hz, 3H), 1.05 (d, J = 7 Hz, 3H), 1.90–2.63 (m, 2H), 3.22 (q, J = 7 Hz, 1H), 5.38 and 5.51 (2d, J = 3 Hz, 2H); $[\alpha]_D^{25}$ +190° (*c* 2.64, $CHCl_3$).

Reduction of (*R*)-**5a** (R^3 = Et) *to* anti-(3*R*,4*R*)-**4a** (R^2 = Et). To a soln of (*R*)-**5a** (R^1 = H, R^2 = Et) (426 mg, 2.3 mmol) in MeOH (4 ml) was added $NaBH_4$ (46 mg, 1.2 mmol) at −10°. After 30 min at −10°, AcOH (0.3 ml, 4.8 mmol) was added and

the resulting soln was stirred at room temp for an additional 30 min. The soln was poured into sat $NaHCO_3$. Extraction with Et_2O followed by filtration through a column of silica gel gave *anti*-(3*R*,4*R*)-**4a** (R^3 = Et) (358 mg, 84%): ^{1}H-NMR (CCl_4) δ 0.11 (s, 9H), 0.88 (t, J = 7 Hz, 3H), 0.94 (d, J = 7 Hz, 3H), 1.20–1.85 (m, 3H), 2.30 (quint, J = 7 Hz, 1H), 3.37 (dt, J = 3, 7 Hz, 1H), 5.45 and 5.65 (2d, J = 3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ −0.9, 9.9, 17.8, 26.5, 45.7, 75.5, 125.6, 155.9; $[\alpha]_D^{25}$ −13.9° (*c* 1.41, $CHCl_3$).

Preparation of syn-(3*S*,4*S*)-**1a** (R^3 = Et). A mixture of *syn*-(3*R*,4*S*)-**4a** (R^3 = Et) (64 mg, 0.34 mmol) and NaH (16 mg, 50% in oil, 0.34 mmol) in THF (1.5 ml) and HMPA (1 ml) was stirred at 30° for 3 h and poured into 3 N HCl. Extraction with hexane and Et_2O (1 : 1) followed by filtration through a column of silica gel afforded *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) (31 mg, 86%); $[\alpha]_D^{25}$ −45.0° (*c* 0.952, $CHCl_3$). The ^{1}H-NMR spectrum of the product was identical in all respects with data described in the literature.[30]

Preparation of anti-(3*S*,4*R*)-**1a** (R^3 = Et). As described above, a mixture of *anti*-(3*R*,4*R*)-**4a** (R^3 = Et) (56 mg, 0.30 mmol) and NaH (14 mg, 0.30 mmol, 50% in oil) in THF (2 ml) and HMPA (1.3 ml) was stirred at 30° for 6 h to give *anti*-(3*S*,4*R*)-**1a** (R^3 = Et) (28 mg, 90%); $[\alpha]_D^{25}$ −12.2° (*c* 0.426, $CHCl_3$). The ^{1}H-NMR spectrum of the product was identical in all respects with data described in the literature.[30]

Conversion of syn-(3*S*,4*S*)-**1a** (R^3 = Et) *to the aldehyde* **11**. A soln of *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) (70 mg, 0.62 mmol), $ClSiEt_3$ (0.12 ml, 0.7 mmol), DMPA (7 mg) and NEt_3 (0.17 ml, 1.2 mmol) in CH_2Cl_2 (0.5 ml) was stirred at room temp for 1 h. Usual workup followed by chromatography on silica gel gave the silyl ether (140 mg, 100%): ^{1}H-NMR (CCl_4) δ 2.01–2.45 (m, 1H), 3.43 (q, J = 6 Hz, 1H), 4.76–5.07 (m, 2H), 5.74 (ddd, J = 7, 11, 18 Hz, 1H); $[\alpha]_D^{25}$ −24.9° (*c* 0.997, $CHCl_3$).

Ozone was introduced into a soln of the above silyl ether (94 mg, 0.4 mmol) in MeOH (3 ml) at −70° for 5 min and then Me_2S (1 ml) was added. After 1 h at room temp, the solvent was removed and the residue was purified by chromatography of silica gel to give the aldehyde **11**. The ^{1}H-NMR spectrum and the specific rotation of **11** were identical with the values reported in the literature: $[\alpha]_D^{27}$ −47.5° (*c* 0.568, $CHCl_3$); enantiomer of **11** (Ref. 18), $[\alpha]_D^{27}$ +49.8° (*c* 2.50, $CHCl_3$).

Conversion of anti-(3*S*,4*R*)-**1a** (R^3 = Et) *to the ester* **15**. To a suspension of KH (1 g, 35% in oil, 9.2 mmol) in THF (15 ml) were added a soln of *anti*-(3*S*,4*R*)-**1a** (R^3 = Et) (480 mg, 4.21 mmol) and $PhCH_2Br$ (0.65 ml, 5.5 mmol) in THF (2 ml). The mixture was stirred at room temp for 1 h and MeOH (0.5 ml) was added at 0° to destroy excess KH. Usual workup followed by chromatography on silica gel afforded the benzyl ether **12** (862 mg, 100%).

The benzyl ether **12** (116 mg, 0.571 mmol) in MeOH (5 ml) was converted to **13** in the same manner as described for the preparation of **11**. The aldehyde **13** in Me_2CO (4 ml) was then oxidized by addding excess Jones reagent to the corresponding acid, from which **14** (80 mg, 84%) was obtained by treatment with excess CH_2N_2 in Et_2O: ^{1}H-NMR (CCl_4) δ 0.92 (t, J = 6 Hz, 3H), 1.16 (d, J = 7.5 Hz, 3H), 1.28–1.68 (m, 2H), 2.68 (quint, J = 7.5 Hz, 1H), 3.57 (s, 3H), 3.42–3.68 (m, 1H), 4.43 (s, 2H), 7.19 (s, 5H); $[\alpha]_D^{25}$ −26.9° (*c* 1.61, $CHCl_3$).

A mixture of **14** (264 mg, 1.1 mmol) and 10% Pd/C (100 mg) in EtOH (15 ml) was stirred overnight. Filtration of the mixture through a column of silica gel afforded **15** (87 mg, 54%). The ^{1}H-NMR spectrum and the specific rotation of **15** were identical with values reported in the literature:[19] $[\alpha]_D^{25}$ −12.2° (*c* 0.824, $CHCl_3$); calculated value for the pure **15** (Ref. 19): $[\alpha]_D^{25}$ −12.9°.

Lactone **19**. To a soln of *syn*-(3*S*,4*S*)-**1a** (R^3 = Et) (520 mg, 4.55 mmol) and i-BuMgCl (11.5 mmol) in THF (17 ml) was added Cp_2TiCl_2 (100 mg, 0.4 mmol) at room temp and the resulting soln was stirred at room temp for 3 h under Ar. The vessel was filled with CO_2 (1 atm) and the soln of **18** was cooled to −60°. Stirring was continued at −60° for 30 min and then at room temp for 4 h. After addition of HCOOH (0.5 ml, 13.7 mmol), the resulting mixture was stirred for 14 h. Usual workup followed by chromatography on silica gel afforded the lactone **19** (350 mg, 54%): ^{1}H-NMR (CCl_4) δ 0.75–2.20 (m, 7H), 2.35 (t, J = 6 Hz, 2H), 4.05 (ddd, J = 3, 6, 8 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 9.5, 11.8, 24.5, 25.6, 26.2, 28.4, 83.8, 171.3.

Alkylation of **19** *to* **20**. To a soln of $LiN(SiMe_3)_2$ in THF (4 ml) and HMPA (0.34 ml), prepared from $HN(SiMe_3)_2$ (0.34 ml, 1.6 mmol) and n-BuLi (1.1 ml, 1.3 mmol, 1.2 M in hexane), was added **19** (92 mg, 0.65 mmol) in THF (2 ml) at −78°. The resulting soln was stirred at −78° for 30 min and at −15° for 1 h. To this soln, MeI (0.14 ml, 2.3 mmol) was added slowly at −78°. After stirring for 1 h at −78°, the soln was poured into sat NH_4Cl. Extraction with Et_2O followed by chromatography on silica gel afforded **20** (87 mg, 86%): ^{1}H-NMR (CCl_4) δ 0.99 (d, J = 6.6 Hz, 3H), 1.00 (t, J = 7.2 Hz, 3H), 1.22 (d, J = 7 Hz, 3H), 1.35–2.70 (m, 6H), 4.09 (ddd, J = 2.6, 5.8, 8.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 9.7, 11.1, 17.7, 25.4, 29.2, 31.2, 35.8, 85.2, 174.2; $[\alpha]_D^{25}$ −45.5° (*c* 0.875, $CHCl_3$).

(4*S*,6*S*,7*S*)-*Serricornin* (**16**). To a soln of **20** (90 mg, 0.58 mmol) in THF (3 ml) was added a soln of EtMgBr (0.58 mmol) in THF (0.4 ml) at −40°. The resulting soln was stirred for 2 h and sat NH_4Cl was added. Extraction with pentane followed by evaporation of the solvent afforded the crude serricornin (**16**), which was used for the next reaction without purification to confirm the structure.

Acetate **17**. A soln of the crude **16**, obtained above, in C_5H_5N (0.5 ml) and Ac_2O (0.5 ml) was stirred at room temp for 20 h. Usual workup followed by chromatography on silica gel gave **17** (90 mg, 68% from **20**). The spectral data (^{1}H- and ^{13}C-NMR) of **17** were in good agreement with data reported for the acetate derived from natural serricornin.[21b]

Alcohol **23**. To a soln of (*R*)-**3c** (500 mg, 1.47 mmol) in Et_2O (30 ml) was added a soln of n-$C_{15}H_{31}MgBr$ (8.4 mmol) in Et_2O (12 ml) at −78°. The resulting soln was stirred at −78° for 2 h and poured into sat NH_4Cl. Extraction with Et_2O followed by chromatography on silica gel afforded **23**: ^{1}H-NMR (CCl_4 + D_2O) δ 0.05 (s, 9H), 0.66–2.26 (m), 1.90–2.26 (m, 1H), 3.15–3.42 (m, 1H), 5.44 and 5.55 (2d, J = 3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 50.6, 73.4, 125.6, 153.9; $[\alpha]_D^{25}$ −0.78° (*c* 1.025, $CHCl_3$).

Alcohol **24**. To a soln of **23** (687 mg, 1.25 mmol) in Me_2CO (25 ml) was added excess Jones reagent at 10° and the resulting mixture was stirred for 30 min at 10°. Usual workup followed by chromatography on silica gel gave the ketone (616 mg, 90%): ^{1}H-NMR (CCl_4) δ 0.05 (s, 9H), 0.70–1.98 (m), 2.01–2.32 (m, 2H), 2.90–3.16 (m, 1H), 5.37 and 5.50 (2d, J = 2.4 Hz, 2H); $[\alpha]_D^{25}$ +54.3° (*c* 1.08, $CHCl_3$).

L-Selectride (1.5 ml, 1.5 mmol, 1 M in THF) was added dropwise to the soln of the above ketone (582 mg, 1.06 mmol) dissolved in THF (15 ml) at −45°. The resulting soln was stirred at −45° for 40 min and then warmed up to 0° over 30 min. Aqueous 3 N NaOH (5 ml) and H_2O_2 (5 ml, 35% in H_2O) was added to the soln. The resulting mixture was stirred at 60° for 1 h and poured into brine. Extraction with hexane and Et_2O (1 : 1) followed by chromatography on silica gel afforded **24** (543 mg, 93%): ^{1}H-NMR (CCl_4 + D_2O) δ 0.05 (s, 9H), 0.70–2.30 (m), 3.19–3.53 (m, 1), 5.50 and 5.62 (2d, J = 3 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 53.2, 73.7, 127.9, 153.9; $[\alpha]_D^{25}$ +9.25° (*c* 1.06, $CHCl_3$).

Alcohol **25**. A mixture of **24** (532 mg, 0.967 mmol) and NaH (45 mg, 0.94 mmol, 50% in oil) in THF (6 ml) and HMPA (18 ml) was stirred at 30° for 1 h to give **25** (397 mg, 86%): ^{1}H-NMR (CCl_4 + D_2O) δ 0.73–2.11 (m), 3.18–3.48 (m, 1H), 4.83–5.16 (m, 2H), 5.57 (ddd, J = 0.9, 11, 16.5 Hz, 1H); $[\alpha]_D^{25}$ +7.83° (*c* 0.971, $CHCl_3$).

Corynomycolic acid (**22**). A mixture of **25** (394 mg, 0.825 mmol), $PhCH_2Br$ (0.3 ml, 1.1 mmol) and KH (140 mg, 1.2 mmol) in THF (10 ml) was stirred at room temp for 2 h and poured into sat $NaHCO_3$ (7 ml). Extraction with hexane and PhH (2 : 1) followed by evaporation of the solvent afforded the benzyl ether of **25**.

Ozone was introduced into a soln of the above benzyl ether dissolved in CH_2Cl_2 (10 ml) and MeOH (0.5 ml) at −17° for 5 min. Usual workup afforded the corresponding aldehyde.

To the aldehyde dissolved in Me_2CO (15 ml) was added excess Jones reagent and the resulting soln was stirred for 30

min at room temp. Usual workup followed by filtration through a column of silica gel gave the acid.

A mixture of the above acid and Pd/C (300 mg, 10%) in AcOEt (30 ml) was stirred at room temp overnight under H_2. Filtration through a column of silica gel followed by evaporation of the solvent gave a white solid, which was purified by chromatography on silica gel to afford **22** (371 mg, 90% from **24**), the physical data of which [$[\alpha]_D^{25}$ + 7.34° (*c* 1.90, $CHCl_3$); m.p. 70–71.5°] were in good agreement with the literature values [29a] [$[\alpha]_D$ + 7.5° (*c* 1.64, $CHCl_3$); m.p. 70.0°]: ^{1}H-NMR ($CDCl_3$) δ 0.5–1.8 (m), 2.14–2.76 (m, 1H), 3.55–3.93 (m, 1H).

The spectral data of (+)-corynomycolic acid methyl ester were as follows: ^{1}H-NMR ($CDCl_3$ + D_2O) δ 0.7–2.0 (m), 2.42 (q, J = 6 Hz, 1H), 3.68 (s, 3H), 3.50–3.80 (m, 1H).

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