Enantioselective Total Synthesis of the (−)-(6*R*,11*R*,14*S*)-Isomer of Colletallol

Sonia J. Amigoni,[†] Loïc J. Toupet,[‡] and Yves J. Le Floc'h*[,†]

Synthèses et Activations de Biomolécules, CNRS ESA 6052, Ecole Nat. Sup. de Chimie de Rennes, av. du Général Leclerc, 35700 Rennes, France, and Groupe Matière Condensée et Matériaux, CNRS URA 804, Université de Rennes, av. du Général Leclerc, 35042 Rennes Cedex, France

Received January 2, 1997[⊗]

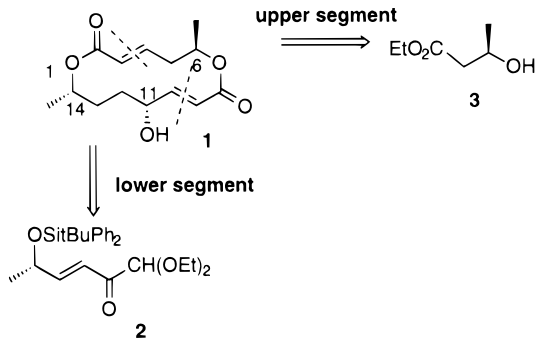
The total synthesis of the (−)-(6*R*,11*R*,14*S*)-isomer of colletallol was achieved in 15 steps. The key steps of the sequence were the building of the macrocycle *via* two consecutive Wittig reactions, the first intermolecular and the second intramolecular, instead of the classical macrolactonization methods.

The family of macrodiolide antibiotics consists of two classes of natural compounds displaying interesting biological properties.[1] The first class consists of 16-membered macrocycles with C_2 symmetry, such as pyrenophorol, pyrenophorin, and vermiculin. The second class comprises those compounds possessing an unsymmetrical 14-membered macrocycle such as colletallol (**1**), colletol, colletoketol, and colletodiol.[2] Quite recently, two novel metabolites possessing a 13-membered macrocyclic ring, bartanol and bartallol, have been also isolated.[3]

Many syntheses of macrodiolides have been reported already.[2] However, in order to obtain detailed structure−activity relashionships in these series, it appears important to design a versatile synthetic scheme giving a unified access to the natural macrodiolides, their stereoisomers, and selected structural analogues. Towards this goal we proposed a strategy involving two key points: (a) the use of two consecutive Wittig reactions to build efficiently the macrodiolide with a complete control of the ring size[4] and (b) the use of a versatile key intermediate (enone **2**) for the control of the stereogenic centers.[5] To fully demonstrate the potential of this approach, we selected the colletallol derivative **1** as a target molecule. Since the natural product (6*R*,11*R*,14*R*) has been already prepared and was found biologically inactive, its (6*R*,11*R*,14*S*) isomer was chosen in order to start some structure−activity data in this family.

Our strategy was clearly formulated in previous papers.[2,4−6] The retrosynthetic Scheme 1 shows the two fragments that join by the means of two successive Wittig reactions. The *lower segment* can be prepared from the polyfunctional enone **2**, for which the synthesis and asymmetric reduction were described recently.[5] The

Scheme 1



upper segment is easily accessible in two steps from commercial (*R*)-ethyl 3-hydroxybutanoate (**3**).

Results and Discussion

The purpose of this paper is to report the total synthesis of the colletallol isomer **1**. One of the key points during the synthesis was the protection of the alcohol function at C_{11}: the *p*-anisyl group proved to be the best choice since it is easily introduced by a Mitsunobu-type procedure and is efficiently removed under mild conditions during the last step.

The synthesis started with the preparation of the protected enone **2**[5] followed by a diastereoselective reduction with the oxazaborolidine derived from (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine and bis(trifluoroethyl) *n*-butylboronate according to Corey and Link.[7] This procedure was simpler and easier to reproduce than the initially described CBS method[8] (Scheme 2).

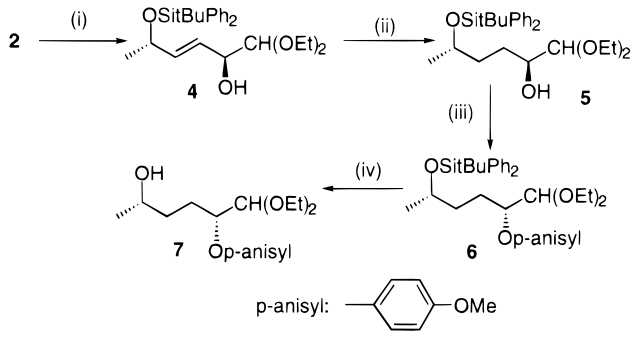
This reduction by BH_3−Me_2S as the reductant and with 1 equiv of oxazaborolidine at rt in THF afforded allylic alcohol **4** (86%) in 95% de. The (*S*)-configuration of the newly created asymmetric carbon was inferred later by an X-ray structural analysis of the target compound **1**. On the basis of the mechanistic studies of Corey et *al.*,[9] we have to consider the acetal group as the smaller one although this statement seems to be counterintuitive. This could be explained by the possible steric hindrance during the reaction between the phenyl groups of the catalyst and those of the protecting group

[†] CNRS ESA 6052.
[‡] CNRS URA 804.
[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Omura, S. *Macrolide Antibiotics: Chemistry, Biology and Practice*; Academic; New York: 1984; pp 538−541.
(2) For full documentation about macrodiolides up to 1995, see: Amigoni, S. J. Ph.D. Thesis, Rennes I University, 1996, and Le Floc'h, Y.; Dumartin, H.; Grée R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 114−118.
(3) Hanson, K.; O'Neill, J. A.; Simpson, T. J.; Willis, C. L. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2493−2497.
(4) Yvergnaux, F.; Le Floc'h, Y.; Grée, R. *Tetrahedron Lett.* **1989**, *30*, 7397−7398. Le Floc'h, Y.; Yvergnaux, F.; Grée, R. *Bull. Soc. Chim. Fr.* **1992**, *129*, 62−70.
(5) Dumartin, H.; Le Floc'h, Y.; Grée, R. *Tetrahedron Lett.* **1994**, *35*, 6681−6684. Contrary to an earlier report from one of us, the reduction of enone **2** with the (*S*)-CBS reagent gave an allylic alcohol with (*S*)-configuration; the right columns of Tables 1 and 2 in the cited article thus concern the ratio 7/6 and not 6/7.
(6) Dommerholt, L. J.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1991**, *32*, 1495−1498.
(7) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 4141−4144.
(8) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611−614.
(9) Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429−3430.

S0022-3263(97)00020-0 CCC: $14.00

Scheme 2[a]



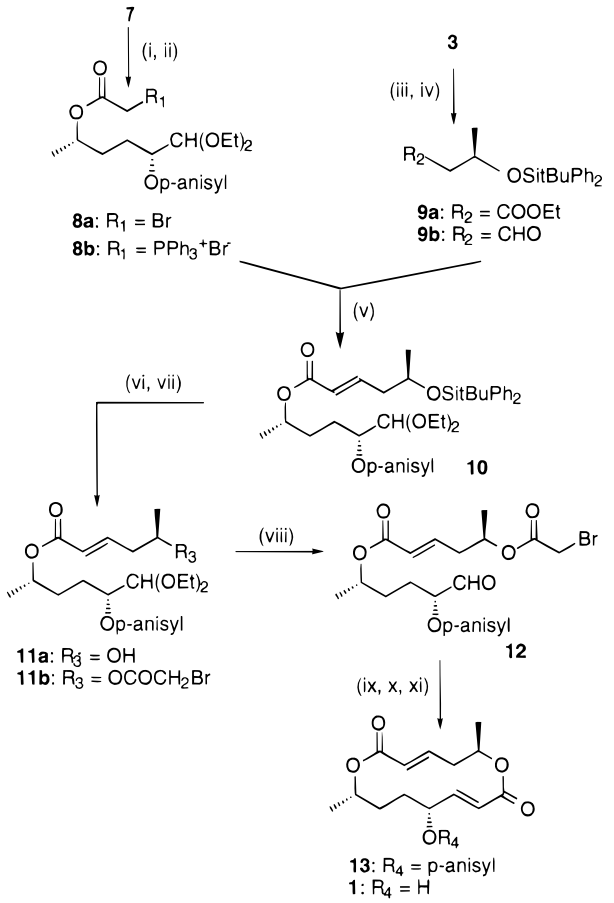
[a] (i) (*S*)-CBS-nBu, BH_3·Me_2S, THF, rt (86%); (ii) H_2, Pd/C 10%, AcOEt, rt (68%); (iii) *p*-$MeOC_6H_4OH$, PPh_3, DEAD, THF, 80 °C (85%); (iv) $nBu_4N^+F^-$, THF, rt (81%).

on the γ-hydroxyl function of enone **2**. This hypothesis did not find any confirmation in the literature. Allylic alcohol **4** was then hydrogenated under standard conditions (10% Pd/C) in good yield to give the saturated alcohol **5**. It was necessary to protect the free secondary hydroxyl group. After many studies, the protection of this alcohol **5** as a *p*-anisyl ether was found to be the best solution. We also verified that the deprotection of this secondary alcohol could be achieved in acceptable yield while sparing the various functionalities present in the molecule. According to the literature,[10] *p*-methoxyphenyl ethers can resist various drastic acidic, basic, and oxidative conditions. The formation of *p*-anisyl ethers from secondary alcohols has already been used by Corey and Link[11] to invert an asymmetric carbon. We found that this protection was conveniently achieved *via* a Mitsunobu reaction (PPh_3, DEAD) with *p*-methoxyphenol in THF at 80 °C for 3 h. Compound **6** was obtained in good yield (85%). In agreement with preceding results, this reaction proceeded with inversion of configuration as unambiguously established by ^1H (400 MHz) and ^{13}C (100 MHz) NMR analysis. The comparison of chemical shifts for the H_1, C_3, and C_4 signals of **5** (2*S*,5*S*) and deprotected **6** (2*R*,5*S*) showed that they were diastereomers.

The protected diol acetal **6** was submitted to the action of the tetrabutylammonium fluoride to afford **7** (81%). This monoprotected diol possesses two asymmetric centers, each of which can be independently set, and so this basic strategy could be used for the construction of several isomers of macrodiolides such as pyrenophorol and colletallol.

The alcohol **7** (Scheme 3) was esterified using bromoacetyl bromide and pyridine in CH_2Cl_2 at −20 °C to give the bromo ester **8a** (86%) which was converted almost quantitatively into the phosphonium salt **8b** by addition of triphenylphosphine. Concurrently, the commercial (*R*)-ethyl 3-hydroxybutanoate (**3**) was transformed into the corresponding aldehyde **9b** by almost quantitative silylation of the free hydroxyl function under classical conditions ($ClSi^+BuPh_2$, imidazole, DMF, rt)[12] followed by reduction of the ester by DIBALH at −78 °C according to Baker's method[13] to give aldehyde **9b** in 87% yield. The phosphonium salt **8b** was treated with 0.8 equiv of TEA to generate *in situ* the corresponding phosphorane which was condensed with 1.5 equiv of the aldehyde **9b** in CH_3CN to give enoate **10** in good yield (74%). The exclusively (*E*)-configuration of the double bond was established by the large (15.8 Hz) vicinal coupling observed between the olefinic protons. At this stage of the synthesis, the upper segment of the target molecule has been introduced with a new asymmetric center. The cleavage of the silyl ether **10** was next achieved with tetrabutylammonium fluoride in THF (Scheme 3).

Scheme 3[a]



[a] (i) $BrCOCH_2Br$, pyridine, CH_2Cl_2, −20 °C (86%), (ii) PPh_3, CH_3CN, rt (94%); (iii) $ClSi^tBuPh_2$, imidazole, THF, rt (96%), (iv) DIBALH, Et_2O, −78 °C (87%); (v) TEA, CH_3CN, 40 °C (74%); (vi) $nBu_4N^+F^-$, THF, rt (73%); (vii) $BrCOCH_2Br$, pyridine, CH_2Cl_2, −20 °C (90%); (viii) HCOOH, rt (93%); (ix) PPh_3, CH_3CN, rt (quant); (x) TEA, CH_3CN, high dilution, 70 °C (65%); (xi) CAN, CH_3CN/H_2O, 0 °C (70%).

These conditions afforded alcohol **11a** in good yield. Esterification with bromoacetyl bromide proceeded smoothly to afford **11b**. Deprotection of the aldehyde function in neat formic acid for 12 h at rt then yielded **12** (93%) (Scheme 3).

The addition of triphenylphosphine generated the phosphonium salt which was directly dissolved in a large volume of acetonitrile. This dilute solution (4×10^{-2} mol/L) was added over 35 h to a solution of 6 equiv of TEA in CH_3CN heated at 70 °C. These high-dilution conditions allowed the cyclic monomer **13** to be formed exclusively in relatively good yields (65%). This intramolecular

(10) The *p*-methoxyphenyl group has been used in order to protect some primary alcohols: Fukuyama, T.; Laird, A. A.; Hotchkiss, L. M. *Tetrahedron Lett.* **1985**, *26*, 6291−6292. Petitou, M.; Duchaussoy, P.; Choay, J. *Tetrahedron Lett.* **1988**, *29*, 1389−1390. To our knowledge, this is the first time that this group has been used for the protection of a secondary alcohol.

(11) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431−3434.

(12) Hopkins, M. H.; Overman, L. E.; Rishton, G. M. *J. Am. Chem. Soc.* **1991**, *113*, 5354−5365.

(13) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180−5182.

Wittig reaction afforded the (*E*)-alkene as established by the large (15.7 Hz) vicinal coupling between the olefinic protons. The (*E*)-configuration of the double bonds and the configurations of the three asymmetric carbons of the molecule were verified by X-ray crystallographic analysis.

Cleavage of the *p*-anisyl ether with CAN in aqueous acetonitrile at 0 °C afforded the (−)-(6*R*,11*R*,14*S*)-isomer of colletallol **1** in 70% yield; the structure was again unambiguously established by X-ray crystallography.[15]

This total synthesis gave the desired colletallol stereoisomer **1** in 15 steps and 4% overall yield. It is important to note that the enantiomers of the starting building blocks are commercially available and that the two esterifications with bromoacetyl bromide could be achieved using bromoacetic acid under Mitsunobu conditions[14] with inversion of configuration at the asymmetric centers. Similarly, the asymmetric reduction of enone **2** by Corey's (*R*)-oxazaborolidine gives allylic alcohol **4′** (2*R*,5*S*) with the same de as previously reported for the (*S*)-enantiomer and in good yields. Thus this strategy is extremely flexible and should be useful for the preparation of any stereoisomer of colletallol. It could be similarly developed for the synthesis of the symmetrical 16-membered macrodiolides such as pyrenophorol[2] for instance.

Experimental Section

General Procedures. Melting points are uncorrected. Optical rotations were measured at 25 °C. IR spectra were recorded on a FT-IR spectrometer. ^{1}H NMR spectra were recorded at 400 MHz and ^{13}C NMR at 100 MHz in $CDCl_3$. Mass spectra were obtained at 70 eV either in EI mode (HRMS) or using CI/NH_3 (MS). Elemental analyses were performed by the Service de microanalyses (ICSN Gif sur Yvette). All separations were carried out under flash chromatographic conditions on Merck silica gel Geduran Si60 (230−240 mesh) using as eluent mixtures of ether (E) and low-boiling (<60 °C) petroleum ether (PE). CH_2Cl_2 was distilled from P_2O_5, toluene from $CaCl_2$, and THF from sodium/benzophenone.

(2*S*,3*E*,5*S*)-1,1-Diethoxy-5-((*tert*-butyldiphenylsilyl)oxy)-3-hexen-2-ol (4). To a solution of borane in THF (1 M, 0.018 mL, 17.5 mmol) was slowly added at 0 °C 2,2,2-trifluoroethanol (3.5 mL, 47.8 mmol, 2.7 equiv). The mixture was stirred for 20 min at rt, and THF was removed by distillation (70−80 °C). After the residual oil was cooled to rt, tributylborane in THF (1 M, 9.5 mL, 9.5 mmol, 0.5 equiv) and borane in THF (1 M, 0.48 mL, 0.48 mmol, 0.03 equiv) were successively added. The solution was heated at 90 °C for 3 h and the solvent removed by distillation (70−80 °C). Distillation of the crude product *in vacuo* (bp 60−70 °C at 0.1 mmHg) afforded the *n*-butylboronate (3 g, 56%).

To a solution of (*S*)-2-(hydroxydiphenylmethyl)pyrrolidine (0.55 g, 2.2 mmol) in anhydrous toluene (2 mL) was added the boronate (0.65 mL, 4.4 mmol, 2 equiv). The reaction mixture was stirred at rt for 20 min and evaporated. The residue was heated for 1 h 30 min at 130 °C under reduced pressure (0.1 mmHg). Borane−dimethyl sulfide complex (0.45 mL, 4.5 mmol, 2 equiv) and a solution of **2** (1 g, 2.3 mmol, 1 equiv) in THF (2 mL) were successively added at 0 °C. After being stirred for 30 min, the reaction was hydrolyzed with MeOH (2 mL) and 1 N HCl (25 mL) was added. The product was extracted with ether, and the organic layer was washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica gel (E/PE (10/90)) yielded **4** (0.86 g, 86%). ^{1}H NMR: δ 7.70−7.40 (m, 10H), 5.88 (dd, J = 15.6 Hz and 5.4 Hz, 1H), 5.65 (dd, J = 15.6 Hz and 5.4 Hz, 1H), 4.38 (m, 1H), 4.22 (d, J = 6.0 Hz, 1H), 4.10 (m, 1H), 3.90−3.50 (m, 4H), 2.25 (d, J = 3.4 Hz, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR: δ 15.3, 15.4, 19.3, 24.2, 27.0, 63.4, 63.5, 69.6, 72.0, 104.7, 126.2, 127.4, 127.5, 129.5, 134.2, 134.6, 135.9, 136.0, 136.6. IR: 3475.0 cm^{-1}. $[\alpha]^{25}_D = -38.1$ (*c* 4.06; CH_2Cl_2). R_f = 0.45 E/PE (50/50). Anal. Calcd for $C_{26}H_{38}O_4Si$: H, 8.66; C, 70.55. Found: H, 8.64; C, 70.27.

(2*R*,3*E*,5*S*)-1,1-Diethoxy-5-((*tert*-butyldiphenylsilyl)oxy)-3-hexen-2-ol (4′). ^{1}H NMR: δ 7.67−7.36 (m, 10H), 5.85 (dd, J = 15.6 Hz and 5.4 Hz, 1H), 5.70 (dd, J = 15.6 Hz and 5.4 Hz, 1H), 4.35 (m, 1H), 4.16 (d, J = 6.0 Hz, 1H), 4.02 (m, 1H), 3.85−3.45 (m, 4H), 2.16 (d, J = 3.6 Hz, 1H), 1.25 (t, J = 7.0 Hz, 3H), 1.19 (t, J = 7.0 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.08 (s, 9H). ^{13}C NMR: δ 15.3, 15.4, 19.2, 24.2, 26.9, 63.4, 63.7, 69.6, 72.1, 104.8, 126.0, 127.4, 127.5, 129.5, 134.2, 134.5, 135.9, 136.9. IR: 3475.0 cm^{-1}. $[\alpha]^{25}_D = -15.4$ (*c* 4.02; CH_2Cl_2). R_f = 0.45 E/PE (50/50).

(2*S*,5*S*)-1,1-Diethoxy-5-((*tert*-butyldiphenylsilyl)oxy)-2-hexanol (5). A solution of allylic alcohol **4** (1.17 g, 2.6 mmol) in ethyl acetate (50 mL) containing 10% Pd/C (0.11 g, 10% by weight) was stirred overnight at rt under a hydrogen atmosphere (1 atm). The mixture was filtered on silica gel and chromatographed (E/PE (10/90)) to afford **5** (0.8 g, 68%). ^{1}H NMR: δ 7.70−7.40 (m, 10H), 4.19 (d, J = 5.6 Hz, 1H), 3.87 (m, 1H), 3.80−3.52 (m, 4H), 3.45 (m, 1H), 2.19 (d, J = 3.6 Hz, 1H), 1.30−1.80 (m, 4H), 1.22 (t, J = 7.1 Hz, 3H), 1.19 (t, J = 7.1 Hz, 3H), 1.05 (d, J = 5.9 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR: δ 15.4, 19.3, 23.2, 27.0, 35.5, 63.4, 69.8, 72.0, 105.1, 127.4, 127.5, 129.4, 129.5, 134.4, 134.9, 135.9. IR: 3435.0 cm^{-1}. $[\alpha]^{25}_D = -16.8$ (*c* 1.04; CH_2Cl_2). R_f = 0.60 E/PE (50/50). HRMS (EI) for $C_{26}H_{40}O_4Si$ calcd: 341.1573. Found: 341.1574.

(2*R*,5*S*)-1,1-Diethoxy-5-((*tert*-butyldiphenylsilyl)oxy)-2-hexanol (5′). ^{1}H NMR: δ 7.67−7.37 (m, 10H), 4.21 (d, J = 6.1 Hz, 1H), 3.93 (m, 1H), 3.80−3.42 (m, 5H), 2.11 (d, J = 3.7 Hz, 1H), 1.30−1.80 (m, 4H), 1.23 (t, J = 7.2 Hz, 3H), 1.21 (m, 3H), 1.20 (t, J = 7.2 Hz, 3H), 1.1 (s, 9H). ^{13}C NMR: δ 15.4, 19.3, 23.1, 27.0, 35.0, 63.5, 69.4, 71.9, 105.1, 127.4, 127.5, 129.4, 129.5, 134.5, 134.9. IR: 3435.0 cm^{-1}. $[\alpha]^{25}_D = -2.6$ (*c* 3.09; CH_2Cl_2). R_f = 0.60 E/PE (50/50).

(2*R*,5*S*)-1,1-Diethoxy-5-((*tert*-butyldiphenylsilyl)oxy)-2-(4′-methoxyphenoxy)hexane (6). DEAD (0.42 mL, 2.7 mmol, 1.6 equiv) was added dropwise to a solution of alcohol **5** (0.76 g, 1.7 mmol), *p*-methoxyphenol (0.72 g, 5.8 mmol, 3.4 equiv), and triphenylphosphine (0.65 g, 2.4 mmol, 1.5 equiv) in THF (45 mL). The mixture was heated at 90 °C for 3 h and the solvent evaporated. The crude product was extracted with ether (25 mL) and filtered. The solution was dried and concentrated under vacuo. Chromatography on silica gel (E/PE (5/95)) yielded **6** (0.8 g, 85%). ^{1}H NMR: δ 7.80−7.30 (m, 10H), 6.80 (m, 4H), 4.43 (d, J = 5.6 Hz, 1H), 4.04 (m, 1H), 3.84 (m, 1H), 3.76 (s, 3H), 3.85−3.40 (m, 4H), 1.45-1.90 (m, 4H), 1.21 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H), 1.03 (s, 9H). ^{13}C NMR: δ 15.4, 15.3, 19.2, 23.1, 25.5, 27.0, 34.8, 55.7, 63.9, 69.4, 80.5, 103.7, 114.4, 117.5, 127.4, 127.5, 129.4, 134.5, 134.9, 135.9, 153.2, 153.9. IR: 2924.2, 1222.0, and 1103.0 cm^{-1}. $[\alpha]^{25}_D = -10.2$ (*c* 0.98; CH_2Cl_2). R_f = 0.95 E/PE (50/50). Anal. Calcd for $C_{33}H_{46}O_5Si$: H, 8.42; C, 71.96. Found: H, 8.51; C, 72.08.

(2*R*,5*S*)-1,1-Diethoxy-2-(4′-methoxyphenoxy)-5-hexanol (7). To a solution of compound **6** (0.8 g, 1.5 mmol) in THF (65 mL) was added a solution of tetrabutylammonium fluoride in THF (1 M, 5.7 mL, 5.7 mmol, 3.8 equiv) at −20 °C. The mixture was warmed up to rt and stirred for 3 days. The reaction was hydrolyzed with brine (50 mL), and the product was extracted with ether (50 mL). The organic layer was dried ($MgSO_4$) and concentrated. Chromatography of the residual oil on silica gel (E/PE (50/50)) afforded **7** (0.37 g, 81%). ^{1}H NMR: δ 6.86 (m, 4H), 4.50 (d, J = 5.1 Hz, 1H), 4.16 (m, 1H), 3.80 (m, 1H), 3.76 (s, 3H), 3.75−3.50 (m, 4H), 1.60−2.00 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 15.3, 15.4, 19.2, 23.4, 26.2, 35.0, 55.7, 64.1, 68.0, 80.3, 103.7, 114.6, 117.4, 153.0, 154.1. IR:

(14) Mitsunobu, O. *Synthesis* **1981**, 1−28. Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491.

(15) The author has deposited atomic coordinates for structures **1** and **13** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

3450.5 cm^{-1}. $[\alpha]^{25}_D = +24.8$ (*c* 1.01; CH_2Cl_2). $R_f = 0.15$ E/PE (50/50). Anal. Calcd for $C_{17}H_{28}O_5$: H, 9.04; C, 65.34. Found: H, 9.03; C, 65.08.

Bromoacetic Acid, (2*R*,5*S*)-1,1-Diethoxy-2-(4′-methoxyphenoxy)-5-hexyl Ester (8a). To a solution of alcohol **7** (0.37 g, 1.2 mmol) and pyridine (0.19 mL, 2.3 mmol, 1.9 equiv) in CH_2Cl_2 (15 mL) was added bromoacetyl bromide (0.12 mL, 1.4 mmol, 1.2 equiv). After being stirred for 20 min, at rt the reaction mixture was filtered on silica gel and the solvent evaporated. The residual oil was chromatographed on silica gel (E/PE (10/90)) to yield **8a** (0.44 g, 86%). ^{1}H NMR: δ 6.85 (m, 4H), 4.97 (m, 1H), 4.49 (d, J = 4.5 Hz, 1H), 4.13 (m, 1H), 3.77 (s, 5H), 3.75−3.45 (m, 4H) 1.95−1.55 (m, 4H), 1.25 (d, J = 6.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 15.3, 15.4, 19.7, 25.4, 26.4, 31.3, 55.7, 64.1, 64.2, 73.2, 79.8, 103.4, 114.6, 117.4, 152.9, 154.1, 166.9. IR: 1743.0 cm^{-1}. $[\alpha]^{25}_D = +12.6$ (*c* 0.87; CH_2Cl_2). $R_f = 0.70$ E/PE (50/50). HRMS (EI) for $C_{19}H_{29}BrO_6$ calcd: 432.1147. Found: 432.1151. Anal. Calcd for $C_{19}H_{29}BrO_6$: H, 6.75; C, 52.66. Found: H, 6.73; C, 52.36.

Phosphonium salt 8b. A solution of **8a** (0.4 g, 0.9 mmol) and triphenylphosphine (0.3 g, 1.1 mmol, 1.2 equiv) in acetonitrile (68 mL) was stirred at rt for 24 h. The solvent was evaporated, and the residue washed with ether (3 × 50 mL) to yield **8b** (0.7 g, 94%). ^{1}H NMR: δ 7.80 (m, 15 H), 6.84 (m, 4H), 5.63 (dd, J = 15.5 Hz and 14.3 Hz, 1H), 5.24 (dd, J = 16.3 Hz and 14.2 Hz, 1H), 4.75 (m, 1H), 4.45 (d, J = 5.1 Hz, 1H), 4.03 (m, 1H), 3.75 (s, 3H), 3.75−3.45 (m, 4H), 1.80−1.35 (m, 4H), 1.20 (t, J = 7.1 Hz, 3H), 1.12 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 6.1 Hz, 3H). ^{13}C NMR: δ 15.3, 15.4, 19.2, 25.5, 31.2, 33.5 (d, J_{CP} = 55.7 Hz), 55.7, 64.3, 64.4, 74.7, 79.7, 103.4, 114.6, 117.2, 118.1 (d, J_{CP} = 89.3 Hz), 130.3 (d, J_{CP} = 13.0 Hz), 134.0 (d, J_{CP} = 10.7 Hz), 135.1 (d, J_{CP} = 3.0 Hz), 152.9, 154.0, 164.1 (d, J_{CP} = 3.8 Hz). IR: 1722.8 and 1635.3 cm^{-1}. $[\alpha]^{25}_D = +6.1$ (*c* 1.14; CH_2Cl_2). $R_f = 0.00$ E/PE (50/50). HRMS (FAB) for $C_{37}H_{44}BrO_6P$ calcd: 615.2876. Found: 615.2882.

Ethyl (3*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)butanoate (9a). A solution of ethyl (*R*)-(−)-3-hydroxybutyrate (**3**) (1 g, 7.6 mmol), *tert*-butyldiphenylsilyl chloride (2.5 g, 9.0 mmol, 1.2 equiv), and imidazole (1.3 g, 19.0 mmol, 2.5 equiv) in DMF (70 mL) was stirred for 3 days at rt. Water was added, and the aqueous layer was extracted with ether (100 mL). The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel (E/PE (5/95)) to yield **9a** (2.7 g, 96%). ^{1}H NMR: δ 7.72−7.41 (m, 10H), 4.33 (m, 1H), 4.08 (m, 2H), 2.57 (dd, J = 14.5 Hz and 6.9 Hz, 1H), 2.41 (dd, J = 14.5 Hz and 5.8 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.14 (d, J = 6.3 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR: δ 14.1, 19.2, 23.6, 26.9, 44.7, 60.3, 66.9, 127.5, 129.6, 133.9, 134.3, 135.8, 135.9, 171.5. IR: 1739.0 cm^{-1}. $[\alpha]^{25}_D = -15.0$ (*c* 2.07; CH_2Cl_2). $R_f = 0.90$ E/PE (50/50). Anal. Calcd for $C_{22}H_{30}O_3Si$: H, 8.17; C, 71.31. Found: H, 8.13; C, 71.47.

(3*R*)-3-((*tert*-Butyldiphenylsilyl)oxy)butanal (9b). To a solution of ester **9a** (1 g, 3.4 mmol) in anhydrous ether (2 mL) was added dropwise a solution of DIBALH in toluene (1M, 4 mL, 4.0 mmol, 1.2 equiv) at −78 °C over 1 h. The reaction mixture was stirred for 1 h at −78 °C and hydrolyzed with an aqueous solution of 2 N NaOH (25 mL). The organic layer was washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel (E/PE (5/95)) to afford **9b** (0.75 g, 87%). ^{1}H NMR: δ 9.75 (t, J = 2.0 Hz, 1H), 7.90−7.50 (m, 10H), 4.34 (m, 1H), 2.53 (ddd, J = 15.8 Hz, 6.1 Hz and J = 3.0 Hz, 1H), 2.47 (ddd, J = 15.8 Hz, 5.6 Hz and 2.0 Hz, 1H), 1.17 (d, J = 6.1 Hz, 3H), 1.00 (s, 9H). ^{13}C NMR: δ 19.2, 23.8, 26.9, 52.7, 65.7, 127.6, 127.7, 129.7, 129.9, 133.5, 134.0, 135.8, 202.1. IR 1732.8 cm^{-1}. $[\alpha]^{25}_D = +10.3$ (*c* 0.98; CH_2Cl_2). $R_f = 0.90$ E/PE (50/50). Anal. Calcd for $C_{20}H_{26}O_2Si$: H, 8.03; C, 73.57. Found: H, 8.20; C, 73.31.

(5*R*)-5-((*tert*-Butyldiphenylsilyl)oxy)hex-2-enoate 10. To a solution of phosphonium salt **8b** (0.4 g, 0.50 mmol) and TEA (0.07 mL, 0.46 mmol, 0.8 equiv) in acetonitrile (20 mL) was added the aldehyde **9b** (0.25 g, 0.84 mmol, 1.5 equiv). The mixture was heated at 40 °C for 24 h and the solvent removed. The residual oil was dissolved in ether (25 mL), filtered, and concentrated. Chromatography on silica gel (E/PE (10/90)) gave **10** (0.28 g, 74%). ^{1}H NMR: δ 6.91 (m, 2H), 6.87 (m, 1H), 6.80 (m, 2H), 5.73 (d, J = 15.8 Hz, 1H), 4.96 (m, 1H), 4.48 (d, J = 5.1 Hz, 1H), 4.12 (m, 1H), 3.95 (m, 1H), 3.75 (s, 3H), 3.80−3.40 (m, 4H), 2.30 (m, 2H), 1.78 (m, 4H), 1.21 (m, 6H), 1.12 (t, J = 7.1 Hz, 3H), 1.08 (d, J = 6.1 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR: δ 15.3, 19.2, 19.9, 23.2, 25.7, 26.9, 31.6, 42.1, 55.6, 63.9, 64.0, 68.5, 70.4, 79.9, 103.5, 114.5, 117.4, 123.8, 127.5, 127.6, 129.5, 129.6, 133.9, 134.3, 135.8, 145.2, 153.0, 165.9. IR: 1721.9 and 1651.6 cm^{-1}. $[\alpha]^{25}_D = +30.7$ (*c* 0.65; CH_2Cl_2). $R_f = 0.75$ E/PE (50/50). Anal. Calcd for $C_{39}H_{54}O_7Si$: H, 8.22; C, 70.66. Found: H, 7.98; C, 70.80.

(5*R*)-5-Hydroxyhex-2-enoate 11a. To a solution of compound **10** (0.28 g, 0.42 mmol) in anhydrous THF (4 mL) were added tetrabutylammonium fluoride in THF (1 M, 1.2 mL, 1.2 mmol, 2.8 equiv) and acetic acid (0.07 mL, 1.22 mmol, 2.9 equiv) at −20 °C. The mixture was stirred at rt for 4 days, and the reaction was hydrolyzed with brine (25 mL). The aqueous layer was extracted with ether (50 mL), the organic layer was dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography on silica gel (E/PE (50/50)) to yield **11a** (0.13 g, 73%). ^{1}H NMR: δ 6.92 (m, 3H), 6.80 (m, 2H), 5.83 (d, J = 15.8 Hz, 1H), 4.97 (m, 1H), 4.48 (d, J = 5.1 Hz, 1H), 4.12 (m, 1H), 3.95 (m, 1H), 3.77 (s, 3H), 3.50−3.75 (m, 4H), 2.34 (t, J = 7.4 Hz, 2H), 1.79 (m, 4H), 1.22 (m, 9H), 1.13 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 15.3, 20.0, 23.2, 25.6, 31.6, 41.9, 55.7, 64.1, 66.7, 70.7, 79.9, 103.5, 114.5, 117.4, 124.3, 144.7, 153.0, 154.0, 166.0. IR 3458.6, 1722.0 and 1658.0 cm^{-1}. $[\alpha]^{25}_D = +13.0$ (*c* 0.30; CH_2Cl_2). $R_f = 0.10$ E/PE (50/50). Anal. Calcd for $C_{23}H_{36}O_7$: H, 8.55; C, 65.06. Found: H, 8.25; C, 64.93.

(5*R*)-5-(Bromoacetoxy)hex-2-enoate 11b. To a solution of alcohol **11a** (0.3 g, 0.7 mmol) and pyridine (0.3 mL, 2.5 mmol, 3.5 equiv) in CH_2Cl_2 (20 mL) was added bromoacetyl bromide (0.2 mL, 2.3 mmol, 3 equiv) at −20 °C. The reaction mixture was stirred for 30 min at −20 °C and filtered on silica gel. The residue was concentrated when chromatography on silica gel (E/PE (20/80)) afforded **11b** (0.35 g, 90%). ^{1}H NMR: δ 6.93 (m, 2H), 6.87 (m, 1H), 6.82 (m, 2H), 5.87 (d, J = 15.6 Hz, 1H), 5.07 (m, 1H), 4.99 (m, 1H), 4.49 (d, J = 5.2 Hz, 1H), 4.15 (m, 1H), 3.81 (s, 2H), 3.78 (s, 3H), 3.50−3.78 (m, 4H), 2.50 (m, 2H), 1.80 (m, 4H), 1.31 (d, J = 6.4 Hz, 3H), 1.26 (d, J = 6.4 Hz, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H). ^{13}C NMR: δ 15.2, 15.3, 19.3, 19.9, 25.6, 25.9, 31.5, 38.0, 55.6, 64.0, 70.8, 71.4, 79.9, 103.4, 114.5, 117.3, 124.9, 142.3, 152.9, 153.9, 165.6, 166.6. IR: 1714.8 and 1665.6 cm^{-1}. $[\alpha]^{25}_D = +19.4$ (*c* 0.30; CH_2Cl_2). $R_f = 0.60$ E/PE (50/50). HRMS (EI) for $C_{25}H_{37}BrO_8$ calcd: 544.1671. Found: 544.1664.

Aldehyde 12. To a solution of compound **11b** (0.35 g, 0.64 mmol) in CH_2Cl_2 (1 mL) was added formic acid (0.5 mL, 13.0 mmol, 20 equiv). The mixture was stirred for 12 h, and the solvent and formic acid were removed under vacuo to afford **12** (0.28 g, 93%). ^{1}H NMR: δ 9.71 (d, J = 2.1 Hz, 1H), 6.89 (m, 1H), 6.84 (s, 4H), 5.87 (d, J = 15.6 Hz, 1H), 5.10 (m, 1H), 5.00 (m, 1H), 4.44 (m, 1H), 3.82 (s, 2H), 3.78 (s, 3H), 2.50 (m, 2H), 1.87 (m, 4H), 1.32 (d, J = 6.3 Hz, 3H), 1.28 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 19.5 and 20.0, 26.0, 26.1, 31.0, 38.1, 55.7, 70.1, 71.4, 82.1, 114.9, 116.5, 124.7, 143.0, 151.6, 154.7, 165.6, 166.7, 202.9. IR: 1739.7, 1718.2, 1662.3, and 1597.7 cm^{-1}. $[\alpha]^{25}_D = +50.7$ (*c* 0.67; CH_2Cl_2). $R_f = 0.40$ E/PE (50/50). HRMS (EI) for $C_{21}H_{27}BrO_7$ calcd: 470.0940. Found: 470.0973.

(6*R*,11*R*,14*S*)-*O*-*p*-Anisylcolletallol (13). A solution of aldehyde **12** (0.25 g, 0.56 mmol) and triphenylphosphine (0.2 g, 0.76 mmol, 1.3 equiv) in acetonitrile (50 mL) was stirred overnight at rt. The solvent was removed, and the residue was washed with ether (3 × 50 mL). The crude product (0.4 g, 0.55 mmol) was dissolved in acetonitrile (70 mL) and was added over 40 h to a solution of TEA (0.5 mL, 3.3 mmol, 6 equiv) in acetonitrile (15 mL) heated at 70 °C. The reaction mixture was stirred for 24 h at 70 °C and the solvent removed. The crude product was extracted with ether (50 mL) and concentrated. Chromatography on silica gel (E/PE (10/90)) afforded **13** (0.14 g, 65%). ^{1}H NMR: δ 6.86 (dd, J = 15.8 Hz and 3.9 Hz, 1H), 6.80 (s, 4H), 6.76 (ddd, J = 15.7 Hz, 8.7 Hz and 6.7 Hz, 1H), 6.02 (dd, J = 15.8 Hz and 1.7 Hz, 1H), 5.80 (d, J = 15.7 Hz, 1H), 5.27 (m, 1H), 5.10 (m, 1H), 4.75 (m, 1H), 3.80 (s, 3H), 2.77 (m, 1H), 2.18 (m, 1H), 1.75−1.65 (m, 2H),

1.41 (d, J = 6.5 Hz, 3H), 1.25 (d, J = 6.4 Hz, 3H). ^{13}C NMR: δ 19.6, 20.2, 28.3, 29.0, 37.8, 55.7, 69.2, 70.5, 76.2, 114.7, 116.9, 121.7, 125.0, 143.9, 147.8, 151.2, 154.2, 165.9. IR: 1707.8, 1651.6, and 1595.3 cm^{-1}. $[\alpha]^{25}_{D}$ = −30.5 (*c* 0.59; CH_2Cl_2). R_f = 0.35 E/PE (50/50). Mp: 122 °C. HRMS (EI) for $C_{21}H_{26}O_6$ calcd: 374.1729. Found: 374.1773. Anal. Calcd for $C_{21}H_{26}O_6$: H, 7.00; C, 67.35. Found: H, 6.96; C, 67.28.

(6*R*,11*R*,14*S*)-Isomer of Colletallol (1). To a solution of compound **13** (0.09 g, 0.24 mmol) in acetonitrile/water (12/3) (15 mL) was added CAN (0.3 g, 0.55 mmol, 2 equiv) at −20 °C. The reaction mixture was stirred for 20 min at −20 °C and was extracted with ether. The organic layer was washed with water (2 × 25 mL), dried ($MgSO_4$), and concentrated. Chromatography on silica gel (E/PE (50/50)) gave **1** (0.045 g, 70%). ^{1}H NMR: δ 6.80 (dd, J = 15.8 Hz and 3.6 Hz, 1H), 6.74 (dd, J = 15.3 Hz and 7.4 Hz, 1H), 6.00 (dd J = 15.8 Hz and 2.0 Hz, 1H), 5.77 (d, J = 15.3 Hz, 1H), 5.23 (m, 1H), 5.10 (m, 1H), 4.39 (m, 1H), 2.76 (m, 1H), 2.35 (m, 1H), 1.96 (m, 1H), 1.79 (d, J = 4.1 Hz, 1H), 1.65−1.45 (m, 3H), 1.39 (d, J = 6.6 Hz, 3H), 1.22 (d, J = 6.6 Hz, 3H). ^{13}C NMR: δ 19.4, 20.2, 28.0, 31.0, 37.5, 69.2, 70.2, 70.3, 120.2, 125.0, 143.9, 150.3, 165.9, 166.1. IR: 1715.0 and 1653.6 cm^{-1}. $[\alpha]^{25}_{D}$ = −99.0 (*c* 0.02; CH_2Cl_2). R_f = 0.10 E/PE (50/50). Mp: 72 °C. MS (CI, NH_3): m/z 286.3, 268.3. HRMS (EI) for $C_{14}H_{20}O_5$ (M − $C_2H_4O^{\bullet})^+$ calcd: 224.1048. Found: 224.1034. Anal. Calcd for $C_{14}H_{20}O_5$: H, 7.52; C, 62.66. Found: H, 7.51; C, 62.73.

Acknowledgment. We thank R. Grée and J. Doyon (CNRS ESA 6052) for several helpful discussions of this work. This research was supported by a grant from the French Ministry of Science and Research.

JO970020S