Enantioselective Total Synthesis of (+)-Eutypoxide B

M. Teresa Barros,[†,‡] Christopher D. Maycock,*[,‡,§] and M. Rita Ventura[‡]

Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa, Departamento de Química, 2825 Monte da Caparica, Instituto de Tecnologia Química e Biológica, Rua da Quinta Grande 6, Apartado 127, 2780 Oeiras, and Faculdade de Ciências da Universidade de Lisboa, Departamento de Química, Rua Ernesto de Vasconcelos, 1700 Lisboa, Portugal

Received September 10, 1996[⊗]

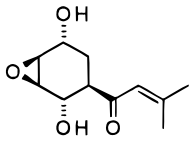
The enantioselective synthesis of (+)-eutypoxide B, a metabolite isolated from the culture medium of the fungus *Eutypa lata*, is described. Two highly stereoselective and efficient sequencial 1,4-additions to enone systems, derived from D-(−)-quinic acid, are the key to the synthesis. The synthesis of a diastereoisomer of (+)-eutypoxide B, was also accomplished.

Introduction

Recently, several highly oxygenated cyclohexane-based metabolites, in many cases epoxides, have been isolated from bacteria, fungi, higher plants, and even molluscs. These compounds have diverse biological activities ranging from antifungal, antibacterial, and antitumor to phytotoxic and enzyme inhibitory.[1−3]

The fungus, *Eutypa lata*, is one of the pathogenic agents responsible for the vineyard die-back disease.[1,2] This disease is known as "dying arm" or "eutypiosis" and is linked to toxic secondary fungal metabolites. *E. lata* is widely distributed in several countries and is known to attack many other woody species.[2]

Eutypoxide B, **1**, is one of the secondary metabolites, isolated from the culture medium of *E. lata*, but has not yet been identified as the cause of the above mentioned disease. For further biological studies, it was necessary to obtain larger quantities by an efficient synthesis. Its enantioselective synthesis, however, poses a challenge in that the core cyclohexane ring is highly substituted and with groups requiring mild reaction conditions. Its racemic synthesis has been reported[2] and also an asymmetric[4] one by a route which is dependent upon a retro-Diels−Alder deprotection of a carbon−carbon double bond.



1

We report here an efficient enantioselective synthesis of (+)-eutypoxide B, **1**, the enantiomer corresponding to the natural product,[2] without recourse to drastic reaction conditions and by employing relatively inexpensive reagents and equipment.

Results and Discussion

The starting material chosen was (−)-quinic acid, **2**, a cyclohexane-based natural substance isolated from the plant species *Cinchona* which has been used successfully in several other syntheses.[5−11] It has the advantage of being readily available and suitably functionalized for conversion to a wide range of interesting structures, particularly polysubstituted cyclohexanes. Our approach capitalized upon the high stereoselectivity of 1,4-additions to α,β-unsaturated ketones derived from quinic acid.[12] We demonstrate here the use of two highly stereoselective sequential 1,4-additions to introduce the required configuration at key positions in the cyclohexane ring. Our initial target was a simple and efficient preparation of the intermediate **4** which was to be the starting point of our synthesis. The first three steps leading to β-hydroxy ketone **3** (Scheme 1) have already been described elsewhere.[13] The enone **4**, $[\alpha]^{20}_{D}$ +137.4 (*c* 1.12, CH_2Cl_2), mp 28−29 °C, was obtained in an excellent yield, 99%, by acetylation of the β-hydroxy ketone **3**, mp 79−80 °C, followed by a very facile[14] *in situ* elimination with diisopropylethylamine. Interestingly, the corresponding benzoate[9] is more stable than the acetate and can be readily isolated. Compound **4** has also been prepared from the same β-hydroxy ketone by Danishefsky and others[12] using sulfonation followed by elimination in a one-pot process.

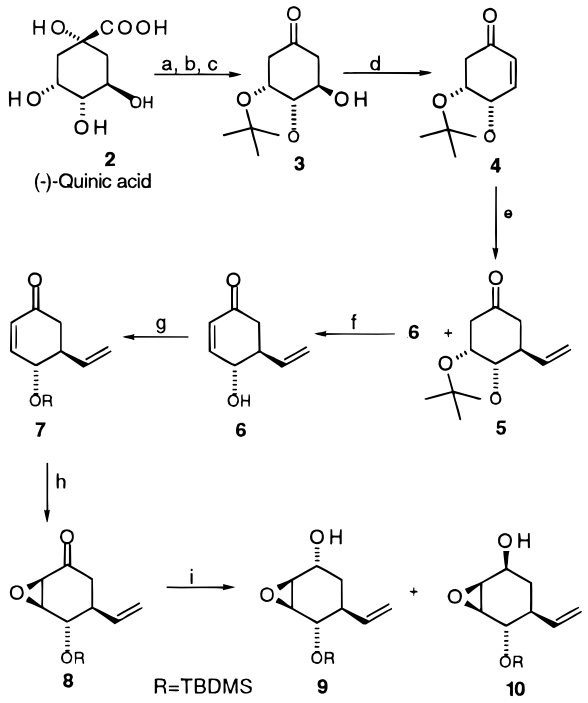
---

† Faculdade de Ciências e Tecnologia Universidade Nova de Lisboa.
‡ Instituto de Tecnologia Química e Biológica.
§ Faculdade de Ciências da Universidade de Lisboa.
⊗ Abstract published in *Advance ACS Abstracts,* May, 1, 1997.

(1) Renaud, J. M.; Tsoupras, G.; Stoeckli-Evans, H.; Tabacchi, R. *Helv. Chem. Acta* **1989**, *72*, 1262.
(2) Defrancq, E.; Gordon, J.; Brodard, A.; Tabacchi, R. *Helv. Chem. Acta* **1992**, *75*, 276.
(3) Kamikubo, T.; Ogasawara, K. *Tetrahedron Lett.* **1995**, *36*, 1685. Nakamori, K.; Natsuura, H.; Ioshihara, A.; Koda, I. *Phytochemistry* **1994**, *35*, 835. Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S. *Tetrahedron* **1979**, *35*, 2861. Ichihara, A.; Kobayashi, M.; Oda, K.; Sakamura, S. *Tetrahedron* **1980**, *36*, 183. Muhlenfeld, A.; Achenbach, H. *Phytochemistry* **1988**, *27*, 3853. Ichihara, A. *Synthesis* **1987**, 207.
(4) Takano; S.; Moriya, M.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1993**, 614.
(5) Eberle, M.; Arigoni, D. *Helv. Chem. Acta* **1960**, *43*, 1508.
(6) Barton, D. H. R.; Gero, S. D.; Maycock, C. D. *J. Chem. Soc., Chem. Commun.* **1980**, 1089.
(7) Elliot, J. D.; Kelson, A. B.; Purcell, N.; Stoodley, R. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2441.
(8) Trost, B. M.; Romero, A. G. *J. Org. Chem.* **1986**, *51*, 2332.
(9) Barros, M. T.; Godinho, L. S.; Maycock, C. D.; Santos, A. G. *Tetrahedron Lett.* **1992**, *33*, 4633.
(10) Kamenecka, T. M.; Overman, L. E. *Tetrahedron Lett.* **1994**, *35*, 4279.
(11) Toyota, M.; Nishikawa, Y.; Fukumoto, K. *Tetrahedron* **1996**, *52*, 10347.
(12) (a) Audia, J. E.; Boisvert, L.; Patten, A. D.; Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1989**, *54*, 3738. (b) Jeroncic, L. O.; Cabal, M.-P.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 387. The cyclohexylidene analogue of compound **4** had been observed previously in work related to ref 6.
(13) Grewe, R.; Nolte, E. *Ann. Chem.* **1952**, *575*, 1. Haslam, E. *Shikimic acid Metabolism and Metabolites*; Wiley-Interscience: New York, 1993.
(14) The ease with which this elimination occurs is probably due to the boat conformation of the cyclohexane ring which is imposed by the isopropylidene acetal ring. In unconstrained systems this elimination occurs less readily. See ref 13.

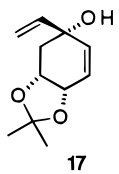
S0022-3263(96)01732-X CCC: $14.00

Scheme 1[a]



[a] (a) Acetone, dry HCl, 89%; (b) Ac_2O, pyridine, 92%; (c) (i) $LiAlH_4$, Et_2O; (ii) $NaIO_4$, H_2O, 5 < pH < 6, 91% (two steps); (d) Ac_2O, $(i\text{-}Pr)_2NEt$, DMAP, CH_2Cl_2, 0 °C, 99%; (e) $(CH{=}CH_2)_2CuCNLi_2$, Et_2O, −30 °C; (f) 0.5 N NaOH, THF, 0 °C; (g) TBDMSCl, $(i\text{-}Pr)_2NEt$, CH_2Cl_2, DMAP, 0 °C/rt 60%; (e−h) *t*-BuOOH, Triton B, THF, 0 °C, 94%; (i) $CeCl_3{\cdot}7H_2O$, $NaBH_4$, methanol, −78 °C/0 °C, 98% (1:1, **9**:**10**).

Our first challenge was to introduce a vinyl group by a 1,4-addition reaction at the α,β-unsaturated ketone. It was thought that a vinyl group would survive the conditions necessary to arrive at a point where an aldehyde group could be generated from it and onto which the five-carbon side chain could be constructed. We envisioned that this aldehyde would be generated by ozonolysis of the double bond, a much simpler and cleaner method than dihydroxylation and oxidation. Our initial efforts to obtain the vinyl ketone **5**, via 1,4-addition, with vinylmagnesium bromide and catalytic or stoichiometric amounts of CuI or CuCN[15] were unsuccessful, due to the insolubility of these Cu(I) salts in ethereal solvents and the partial decomposition of the thermally unstable vinyl cuprate formed. Thus, instead of a regiospecific 1,4-addition of the vinyl group, we obtained a mixture of ketone **5** and the 1,2-addition product **17**, $[\alpha]^{20}_D$ +29.0 (*c* 0.65, CH_2Cl_2) which was difficult to separate.



17

In an attempt to avoid this side reaction, we used the readily available, crystalline complex, $Me_2S(CuBr)$.[16] This complex is soluble in mixtures of Me_2S and ethereal solvents, and the sulfide ligand, Me_2S (bp 37 °C), is easily separated from reaction products. We used a stoichiometric quantity of $Me_2S(CuBr)$ to try to prevent the occurrence of uncomplexed vinylmagnesium bromide that led to compound **17**. The temperature was kept below −20 °C, because of the thermal instability of the vinyl cuprate reagent, and above −40 °C to achieve a reasonable reaction rate between the vinylmagnesium bromide and Cu(I). We obtained the 1,4-addition product as the sole isolable material, but the yield was only 39%, since partial decomposition of the starting material had occurred.

To improve the yield of this step, we took advantage of the greater stability and reactivity of the higher-order cyanocuprate[17] $(CH{=}CH_2)_2Cu(CN)Li_2$. To prepare this reagent *in situ*, we also had to prepare the vinyllithium necessary for this reaction[18] by transmetalation on tetravinyltin. The conjugate addition of $(CH{=}CH_2)_2Cu(CN)Li_2$ to enone **4** afforded the ketone **5** $[\alpha]^{20}_D$ +26.3 (*c* 2.05, CH_2Cl_2) and its base-induced elimination product **6**. No addition to this double bond was observed even though an excess of organocuprate was used so we assume that elimination occurred after the reagent had been destroyed. Since **6** was the next required product it was unnecessary to optimize this reaction or to purify this mixture. Thus, it was treated with a catalytic quantity of aqueous 0.5 N NaOH in THF, to convert all the remaining ketone **5** into the enone **6**, $[\alpha]^{20}_D$ −109.3 (*c* 1.85, CH_2Cl_2), in virtually quantitative yield. Without purification, we proceeded to the protection of the hydroxyl group (Scheme 1) to obtain the silyl ether **7**, $[\alpha]^{20}_D$ −142.9 (*c* 0.96, CH_2Cl_2), in 82% yield. The overall yield of these three steps, without purification of the intermediates, was 60%, the lowest individual yield being from the 1,4-addition reaction. In all previous uses of these compounds as intermediates,[10−12] one of the double bonds has been saturated such that the elimination served as a deoxygenation method. This synthesis used the functionality to the fullest, and both double bonds were used to introduce chirality and to functionalize the ring.

On exposure to *t*-BuOOH and a catalytic amount of Triton B, in THF,[19] **7** afforded exclusively the epoxide **8**, $[\alpha]^{20}_D$ −9.24 (*c* 1.12, CH_2Cl_2), in 94% isolated yield, revealing the influence of the adjacent bulky TBS ether group on the selectivity of the epoxidation which arises from a second 1,4-addition. The use of the less bulky epoxidizing agent, hydrogen peroxide, in place of the above, resulted in the loss of diastereofacial selectivity, producing a mixture of epoxides which proved difficult to separate.

Reduction of the ketonic carbonyl group with sodium borohydride in methanol was readily achieved, and we obtained the two diastereoisomers **9**, $[\alpha]^{20}_D$ +5.9 (*c* 1.74, CH_2Cl_2), and **10**, $[\alpha]^{20}_D$ −48.7 (*c* 0.875, CH_2Cl_2), in high yield with a diastereoselectivity of 40:60 (ratio **9**/**10**, 0.7). This ratio demonstrates the somewhat unexpected low influence of the *t*-$BuMe_2Si$ group on the diastereoselectivity of the reduction.

(15) House, H. O.; Respess, W. L.; Whitesides, G. M. *J. Org. Chem.* **1966**, *31*, 3128. Kretchemer, R. B.; Mihelich, E. D.; Waldron, J. J. *J. Org. Chem.* **1972**, *37*, 4483.

(16) House, H. O.; Chu, C.-Y.; Wilkins, J. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460. Shea, K. J.; Pham, P. Q. *Tetrahedron Lett.* **1983**, *24*, 1003. House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 3893.

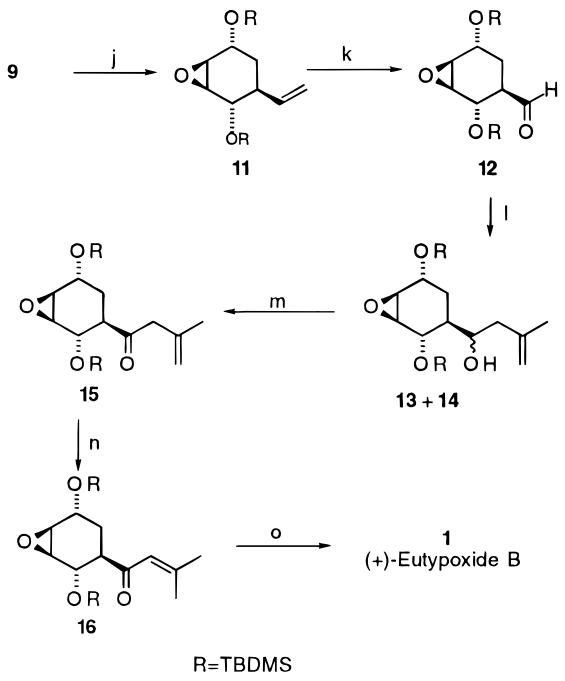
(17) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005. Lipshutz, B. H. *Synthesis* **1987**, 325.

(18) Nugent, W. A.; Hobbs, F. W., Jr. *Organic Syntheses*; Wiley: New York, 1993; Coll. Vol. VIII, p 112.

(19) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Burke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5773. Yang, N. S.; Finnegan, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5845.

(20) Barros, M. T.; Alves, C. M.; Santos, A. G.; Godinho, L. S.; Maycock, C. D. *Tetrahedron Lett.* **1995**, *36*, 2321.

Scheme 2[a]



[a] (j) TBDMSCl, CH_2Cl_2, $(i\text{-}Pr)_2NEt$, DMAP, 0 °C/rt, 99%; (k) (i) O_3, CH_2Cl_2, −78 °C; (ii) PPh_3, Et_2O, rt, 92% (two steps); (l) $CH_3C(CH_2)CH_2MgCl$, Et_2O, 0 °C, 96%; (m) periodinane, pyridine, CH_2Cl_2, 0 °C/rt, 99%; (n) DBN, CH_2Cl_2, rt, 99%; (o) Bu_4NF, THF, cat. H_2O, rt, 93%.

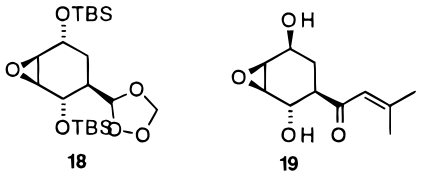
We attempted to improve the diastereoselectivity of this reduction, by adding 1 equiv of cerium(III) chloride,[20] but we only succeeded in increasing the ratio **9**/**10** of the two alcohols to unity. By performing the reduction with zinc borohydride, the diastereomeric ratio was raised to about 60:40, **9**:**10**, but the yield was unsatisfactory. This improvement was probably due to complexation of the zinc[21] to the epoxide oxygen thus delivering the hydride to the upper face. However, since the secondary products appeared to be derived from epoxide ring opening we suspect that an interaction between the basic epoxide oxygen atom with the acidic zinc is beneficial for the reduction but also promotes epoxide ring opening and is thus detrimental to the overall yield of the required product. We have not studied this reaction exhaustively, but we believe that it is possible to increase the diastereoselectivity of this reduction by varying the reaction conditions. Although not attempted Mitsunobu technology should provide a means of converting **10** to **9** in two steps.

The reduced compound also provided us with an opportunity to assign the signals for H-2 and H-3 in the NMR spectrum. In compound **8** the corresponding ^1H NMR signals indicated vicinal proton coupling only between themselves (H-2 and H-3). Upon reduction to alcohols **9** and **10** additional coupling was observed for one of the proton signals (H-2) along with an expected upfield shift compared to **8**.

The two diastereoisomers were separated, and the alcohol **9** was protected with TBDMSCl, in the presence of diisopropylethylamine and DMAP, to afford fully protected compound **11**, $[\alpha]^{20}_D$ +10.3 (*c* 1.23, CH_2Cl_2), in 99% yield (Scheme 2).

(21) Cerium could also function in a similar way to zinc but without the consequent ring opening.

Having achieved this biprotected cyclic nucleus, we then proceeded to build up the side chain. Ozonolysis of **11** produced the expected intermediate ozonide **18** which proved to be surprisingly stable and could be isolated readily. Both diastereomers were evident from the NMR spectrum and in fact the ozonolysis was slightly diastereoselective. This ozonide was resistant to extended periods in the presence of excess dimethyl sulfide and zinc/acetic acid but was reduced rapidly to the aldehyde **12**, $[\alpha]^{20}_D$ −3.1 (*c* 1.03, CH_2Cl_2) by triphenylphosphine in 92% overall yield for the two steps. No simultaneous attack at the epoxide oxygen was observed.



Owing to the insolubility of the inexpensive Grignard reagent, (2-methyl-1-propen-3-yl)magnesium chloride in ethereal solvents, the exact concentration of the reagent was difficult to determine. An excess of the organomagnesium reagent produced undesirable products formed by epoxide ring opening. Thus, the addition to the aldehydic carbonyl of **12** had to be carried out with precaution in order to assure the exclusive formation of the two diastereoisomeric alcohols **13** and **14**. By careful addition of the Grignard with monitoring, we were able to obtain a good yield of the two separable diastereomers **13** $[\alpha]^{20}_D$ −14.3 (*c* 1.295, CH_2Cl_2) and **14** $[\alpha]^{20}_D$ −7.2 (*c* 0.57, CH_2Cl_2), mp 51−52 °C. At this stage in our asymmetric synthesis, we had obtained, with good stereocontrol up to the reduction step (**8** to **9**), compounds with six chiral centers.

Oxidation of the mixture of **13** and **14** was accomplished with periodinane, a mild and selective reagent for the oxidation of primary and secondary alcohols to aldehydes and ketones.[22] By performing the reaction in the presence of pyridine and using the thiosulfate workup, with sodium bicarbonate buffer,[22] it was possible to maintain nearly neutral conditions throughout the entire reaction and isolation sequence. In this way, we obtained compound **15**, $[\alpha]^{20}_D$ −7.4 (*c* 0.81, CH_2Cl_2), mp 59−60°, in almost quantitative yield.

For the quantitative isomerization of **15** to give the α,β-unsaturated ketone **16**, $[\alpha]^{20}_D$ −6.1 (*c* 1.12, CH_2Cl_2), we used a catalytic amount of DBN, instead of 1 equiv of the related base DBU, as was reported.[4] These last three steps could be carried out successfully without purifications which reduced significantly the time consumed for this synthesis.

Finally, the removal of the two TBS groups was achieved under nonacidic conditions and in excellent yield using Bu_4NF in THF containing a small amount of water. This afforded (+)-eutypoxide B, **1**, $[\alpha]^{23}_D$ +57.3 (*c* 0.84, anhydrous $CHCl_3$) (lit.[4] (-)-eutypoxide (*ent*-**1**), $[\alpha]^{23}_D$ −56.6 (*c* 0.68, $CHCl_3$)) identified by spectroscopic comparison[2] as the natural product isolated from the fungus *E. lata*. This deprotection afforded several byproducts when carried out under anhydrous conditions with the same reagent. On the other hand no reaction occurred when

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1987**, *48*, 4155. Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277.

(23) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press: New York, 1980.

this transformation was attempted using more than a trace amount of water.

The epimeric alcohol **10**, was converted, following the same reaction sequence, into compound **19**, $[\alpha]^{20}_D$ −13.7 (c. 0.52, CH_2Cl_2), a previously unreported diastereoisomer of **1**, in good overall yield.

Conclusion

The fungal metabolite eutypoxide B has been synthesized in a stereospecific manner using an efficient transformation of quinic acid. This synthesis demonstrates that similar technology may be useful for the synthesis of analogous metabolites. We are attempting such syntheses as well as studying the 1,4-additions to other, quinic acid derived, cyclohexenone systems in order to develop routes to the syntheses of the enantiomers of some of the intermediates described here.

Experimental Section

General. Melting points were determined with a capillary apparatus and are uncorrected. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with chemical shift values (δ) in ppm downfield from tetramethylsilane, and ^{13}C NMR spectra were obtained at 100.61 MHz in $CDCl_3$. Microanalyses were performed by the ITQB analytical services using a combustion apparatus. FT-IR (ν, cm^{-1}): liquid samples were measured as thin films on NaCl windows. Medium pressure preparative column chromatography: silica gel Merck 60 H. Preparative TLC: silica gel Merck 60 GF_{254}. Analytical TLC: Aluminum-backed silica gel Merck 60 F_{254}. Specific rotations ($[\alpha]^{20}_D$) were measured on an automatic polarimeter. Reagents and solvents were purified and dried according to ref 23. All the reactions were carried out in an inert atmosphere (argon), unless otherwise indicated.

(4*S*,5*R*)-4,5-(Isopropylidenedioxy)cyclohex-2-en-1-one (4). To a solution of **3** (1.5 g, 8 mmol) in CH_2Cl_2 (6 mL), at 0 °C, was added a catalytic amount of 4-(dimethylamino)pyridine (DMAP), diisopropylethylamine (2.8 mL, 16 mmol, 2 equiv), and acetic anhydride (0.91 mL, 9.6 mmol, 1.2 equiv). After stirring for 3 h at 0 °C all of the starting material had been consumed. The reaction mixture was washed with saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and concentrated. Kugelrohr distillation gave 1.34 g (99%) of **4**, as a colorless oil that slowly crystallized as white needles. $[\alpha]^{20}_D$ +137.4 (*c* 1.12, CH_2Cl_2) (lit. $[\alpha]_D$ +147.5 (*c* 0.48, $CHCl_3$)). mp 28−29 °C (lit. 39−40 °C). ^{1}H NMR ($CDCl_3$): δ 6.83 (1H, d, J = 10.4 Hz); 6.20 (1H, d, J = 10.4 Hz); 4.90 (1H, s); 4.86 (1H, s); 3.10 (1H, d, J = 17.6 Hz); 2.97 (1H, dd, J = 17.6 Hz, J = 4.1 Hz); 1.55 (3H, s); 1.54 (3H, s). ^{13}C NMR ($CDCl_3$): δ 195.3; 145.8; 128.8; 109.9; 73.3; 71.0; 38.7; 27.7; 26.5. FT-IR (film): 2989, 2935, 2910 (C−H); 1682 (C=O, α,β-unsat ketone). Anal. Calcd for $C_9H_{12}O_3$ (168.19419): C 64.27, H 7.19. Found: C 64.03, H 7.23.

(3*R*,4*S*,5*R*)-3,4-(Isopropylidenedioxy)-5-vinylcyclohexan-1-one (5). A three-necked, round-bottomed flask was flame-dried and fitted with an internal thermometer. Under a positive pressure argon atmosphere, the flask was charged with tetravinyltin (1.937 mL, 0.011 mol) and anhydrous ether (48.1 mL). The solution was cooled to 0 °C, and methyllithium in ether (24.18 mL, 1.6 M, 0.039 mol) was slowly added to the stirred solution. After 15 min, the vinyllithium mixture was cooled to −78 °C for 20 min. The septum on one neck was briefly removed, and copper(I) cyanide (1.846 g, 0.021 mol) was added all at once. The bath and reaction were allowed to warm slowly over about 1 h, until the internal temperature attained −30 °C. A solution of **4** (1.3 g, 7.7 mmol) in 3.12 mL in ether was added dropwise to the cuprate at −30 °C. Saturated aqueous NH_4Cl was slowly added while the temperature of the system was allowed to rise. The mixture was extracted with ether, dried ($MgSO_4$), and evaporated to yield a mixture (0.825 g) of **5** and **6**, which was used without further purification in the next step. In order to characterize compounds **5** and **6**, a sample of the previous mixture was purified by preparative TLC (AcOEt/hexane 4:6) to afford 0.039 g (34%) of **5** and 0.24 g (29%) of **6**, both as colorless oils. Compound **5**: $[\alpha]^{20}_D$ +26.3 (*c* 2.05, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 5.89−5.80 (1H, m); 5.22 (1H, d, J = 10.0 Hz); 5.14 (1H, d, J = 17.8 Hz); 4.61−4.58 (1H, q,); 4.38 (1H, dd, J = 7.0 Hz, J = 3.8 Hz); 2.88 (1H, m); 2.68−2.59 (3H, m); 2.37 (1H, dd, J = 17.7 Hz, J = 5.6 Hz); 1.48 (3H, s); 1.37 (3H, s). ^{13}C NMR ($CDCl_3$): δ 208.3; 137.1; 116.7; 108.1; 75.3; 72.3; 41.4; 40.4; 38.4; 26.5; 23.9. FT-IR (film): 2987,2935, 2912 (C−H); 1718 (C=O). Compound **6**: $[\alpha]^{20}_D$ -109.3 (*c* 1.85, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): 6.96 (1H, d, J = 10.3 Hz); 6.01 (1H, d, J = 10.0 Hz); 5.80 (1H, m); 5.31 (2H, d, J = 5.5 Hz);4.35 (1H, d, J = 8.6 Hz); 2.72 (1H, m); 2.58 (1H, dd, J = 16.7 Hz, J = 4.0 Hz); 2.35 (1H, dd, J = 16.9 Hz, J = 13.3 Hz). FT-IR (Film): 3433 (O=H); 2876 (C=H); 1685 (C=O, α,β-unsat ketone).

(4*S*,5*R*)-4-Hydroxy-5-vinyl-2-cyclohexen-1-one (6). To a solution of **5** (1.476 g, 7.5 mmol) in THF, at 0 °C, was added a catalytic amount of aqueous NaOH (0.5 N). The mixture was stirred at 0 °C until all the starting material had been consumed. Saturated aqueous NH_4Cl was added, and the mixture was extracted with ethyl ether. The organic extracts were dried ($MgSO_4$) and concentrated. The residue obtained (0.990 g) was used in the next reaction without further purification. The NMR spectrum of **6** is described in the previous experiment.

(4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-5-vinyl-2-cyclohexen-1-one (7). To a solution of **6** (0.831 g, 6.0 mmol) in CH_2Cl_2 (4.16 mL), at 0 °C, were added diisopropylethylamine (2.6 mL, 15.5 mmol, 2.5 equiv), a catalytic amount of DMAP, and *tert*-butyldimethylsilyl chloride (TBDMSCl) (1.812 g, 12 mmol, 2 equiv) in CH_2Cl_2 (4.16 mL). The solution was stirred at rt for 2 days. Water was then added, and the mixture was vigorously stirred for 15 min and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (AcOEt/hexane 2/98) to afford 1.24 g (82%) of **7** as a colorless oil. $[\alpha]^{20}_D$ −142.9 (*c* 0.96, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 6,78 (1H, dd, J = 10.2 Hz, J = 2.1 Hz); 5.95 (1H, d, H-2); 5.821 (1H, m); 5.16 (1H, s); 5.11 (1H, d, J = 9.2 Hz); 4.27 (1H, tt); 2.75 (1H, m); 2.58 (1H, dd, J = 16.4 Hz, J = 4.0 Hz); 2.32 (1H, dd, J = 16.5 Hz, J = 12.6 Hz); 0,92 (9H, s); 0.12, 0.11 (6H, 2s). FT-IR (Film): 1693 (C=O, α,β-unsat ketone).

(2*S*,3*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-5-vinylcyclohexan-1-one (8). To a solution of **7** (0.723 g, 2.9 mmol) in THF (6 mL) at 0 °C was added Triton B (*N*-benzyltrimethylammonium hydroxide, 40 wt % solution in methanol, 0.069 mL, 0.023 mmol, 0.058 equiv) and *t*-BuOOH (*tert*-butyl hydroperoxide anhydrous, 3.0 M solution in isooctane, 4.77 mL, 14.3 mmol, 5 equiv). After 2 h at 0 °C, water and saturated aqueous NH_4Cl were added, and the mixture was extracted with ethyl ether, dried ($MgSO_4$), and evaporated to give a colorless residue, which was purified by column chromatography. Elution with AcOEt/hexane 2/98 afforded **8** (0.723 g, 94%) as a colorless oil. $[\alpha]^{20}_D$ −9.24 (*c* 1.12, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 5.76 (1H, m); 5.11 (1H, d, J = 7.2 Hz); 5.02 (1H, s); 3.99 (1H, d, J = 7.2 Hz); 3.46 (1H, d, J = 3.7 Hz); 3.27 (1H, d, J = 3.6 Hz); 2.57 (2H, m); 2.19 (1H, d, J = 10.3 Hz); 0.91 (9H, s); 0.15, 0.10 (6H, 2s). FT-IR (film): 1728 (C=O, ketone).

(1*R*,2*S*,3*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-1-hydroxy-5-vinylcyclohexane (9) and (1*S*,2*S*,-3*R*,4*S*,5*R*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2,3-epoxy-1-hydroxy-5-vinylcyclohexane (10). To a solution of **8** (0.544 g, 2.0 mmol) in methanol (6 mL) was added $CeCl_3 \cdot 7H_2O$ (0.775 g, 2.08 mmol, 1 equiv). At −78 °C was added $NaBH_4$ (0.308 g, 8.14 mmol, 4 equiv). The reaction mixture was stirred at this temperature for 30 min and then at 0 °C for 30 min. Saturated NH_4Cl was added, followed by extractions with ethyl ether. The organic extracts were dried ($MgSO_4$), and the solvent was evaporated to yield a residue. Purification by column chromatography (AcOEt/hexane 1:9) afforded 0.268 g of **9** and 0.262 g of **10** (98% yield, dr 1:1), both as colorless oils. Compound **9**: $[\alpha]^{20}_D$ +5.9 (*c* 1.74, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 5.70 (1H, m); 5.08 (1H, d, J = 7.0 Hz); 5.02 (1H, s);

4.32 (1H, t); 3.60 (1H, d, J = 9.0 Hz); 3.20 (1H, s); 3.14 (1H, d, J = 3.4 Hz); 2.28 (1H, m); 1.70 (1H, broad s); 1.54 (2H, m); 0.91 (9H, s); 0.12, 0.07 (6H, 2s). FT-IR (film): 3412 (O-H). Anal. Calcd for $C_{14}H_{26}O_3Si$ (270.44702): C 62.18, H 9.69. Found: C 62.20, H 9.73. Compound **10**: $[\alpha]^{20}_D$ −48.7 (*c* 0.875, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 5.70 (1H, m); 5.06 (1H, s); 5.02 (1H, d, J = 2.9 Hz); 4.14−4.08 (1H, m); 3.59 (1H, d, J = 9.1 Hz); 3.37 (1H, broad s); 3.19 (1H, d, J = 3.8 Hz); 2.00−1.93 (1H, m); 1.87 (1H, broad s); 1.70 (1H, qq); 1.29 (1H, m); 0.90 (9H, s); 0.12, 0.06 (6H, 2s). ^{13}C NMR ($CDCl_3$): δ 139.5; 115.6; 70.4, 68.4; 60.0; 56.5; 46.0; 29.7; 25.7; 18.0; −4.5; −4.7. FT-IR (film): 3410 (O−H).

(1*R*,2*S*,3*R*,4*S*,5*R*)-1,4-Bis[(*tert*-butyldimethylsilyl)oxy]-2,3-epoxy-5-vinylcyclohexane (11). To a solution of **9** (0.335 g, 1.2 mmol) in 3.1 mL of CH_2Cl_2 at 0 °C were added diisopropylethylamine (0.54 mL, 3.2 mmol, 2.5 equiv), a catalytic amount of DMAP, and TBDMSCl (0.367 g, 2.4 mmol, 2 equiv) in 3.1 mL of CH_2Cl_2. The solution was stirred at rt for one day. Water was added, and the mixture was vigorously stirred for 15 min and then extracted with CH_2Cl_2, dried ($MgSO_4$), and concentrated. The residue obtained was purified by column chromatography (AcOEt/hexane 2.5/97.5) to yield 0.428 g (99%) of **11**, as a white solid below 4 °C (at rt it is a colorless oil). $[\alpha]^{20}_D$ +10.3 (*c* 1.23, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 5.71 (1H, m); 5.04 (1H, d, J = 5.7 Hz); 4.91 (1H, s); 4.24 (1H, d); 3.56 (1H, d, J = 9.6 Hz); 3.11 (1H, d, J = 2.9 Hz); 3.06 (1H, broad s); 2.36 (1H, m); 1.43−1.39 (2H, m); 0.92 (18H, 2s); 0.12, 0.11, 0.09, 0.07 (12H, 4s). ^{13}C NMR ($CDCl_3$): δ 140.8; 115.1; 71.4, 65.2; 58.0, 55.3; 39.4; 30.5; 25.8, 25.7; 18.1; −4.4, −4.6, −4.8, −4.9. FT-IR (film): 3080, 2993, 2953, 2930, 2887, 2868 (C−H). Anal. Calcd for $C_{20}H_{40}O_3Si_2$ (384.711): C 62.44, H 10.48. Found: C 62.54, H 10.36.

(1*R*,2*S*,3*R*,4*S*,5*R*)-[2,5-Bis(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexyl]methanal (12). Into a solution of **11** (0.290 g, 0.83 mmol) in 30 mL of CH_2Cl_2 at −78 °C was bubbled ozone till the solution turned blue. The temperature was allowed to rise, and the solvent was evaporated. The residue was dissolved in ethyl ether (6 mL), and triphenylphosphine (0.408 g, 1.6 mmol, 2 equiv) was added. The solution was stirred at rt until all the ozonide had been consumed. The solvent was evaporated, and the residue was purified by column chromatography (AcOEt/hexane 0.5/99.5) to afford 0.295 g (92%) of **12** as a colorless oil. $[\alpha]^{20}_D$ −3.1 (*c* 1.03, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 9.70 (1H, s); 4.27 (1H, broad s); 4.19 (1H, d, J = 8.8 Hz); 3.12−3.09 (2H, m); 2.67 (1H, m); 1.64 (1H, m); 1.48 (1H, m); 0.90, 0.87 (18H, 2s); 0.13, 0.11 (12H, 2s). FT-IR (film): 1728 (C=O, aldehyde). Anal. Calcd for $C_{19}H_{38}O_4Si_2$ (386.68331): C 59.02, H.9.91. Found: C 59.11, H 10.28.

(1*R*)-1-[(1*S*,2*S*,3*R*,4*S*,5*R*)-2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexyl]-3-methyl-3-buten-1-ol (13) and (1*S*)-1-[(1*S*,2*S*,3*R*,4*S*,5*R*)-2,5-bis[(*tert*-Butyldimethylsilyl)oxy]-3,4-epoxycyclohexyl]-3-methyl-3-buten-1-ol (14). To a solution of **12** (0.250 g, 0.65 mmol) in ethyl ether (3 mL) at 0 °C was added, from a syringe, an ethereal suspension of the Grignard reagent, (2-methyl-1-propen-3-yl)magnesium chloride (0.964 mL, 0.64 mmol, 1.1 equiv), in small portions. When the reaction was complete (TLC), saturated aqueous NH_4Cl was added, and the mixture was extracted with ethyl ether, dried ($MgSO_4$), and concentrated. Purification by column chromatography gave 0.275 g (96%) of **13** and **14**. First diastereoisomer (colorless oil): $[\alpha]^{20}_D$ −14.3 (*c* 1.295, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 4.87, 4.81 (2H, 2s); 4.42 (1H, d, J = 1.8 Hz); 3.90 (1H, m); 3.80 (1H, d, J = 9.4 Hz); 3.08 (2H, m,); 2.13 (1H, d, J = 13.7 Hz); 1.99 (1H, dd, J = 13.8 Hz, J = 10.5 Hz; 2.0 (1H, m); 1.76 (3H, s); 1.59 (1H, tt, J = 13.9 Hz, J = 2.8 Hz); 1.23 (1H, m); 0.93, 0.92 (18H, 2s); 0.19, 0.14, 0.13, 0.11 (12H, 4s). FT-IR (film): 3545 (O−H). Second diastereoisomer (white solid): $[\alpha]^{20}_D$ −7.2 (*c* 0.57, CH_2Cl_2). Mp 51−52 °C. ^{1}H NMR ($CDCl_3$): δ 4.81, 4.78 (2H, 2s); 4.29 (1H, s); 4.01 (1H, dd); 3.91 (1H, d, J = 9.3 Hz); 3.12 (1H, d, J = 3.2 Hz); 3.03 (1H, t); 2.20 (1H, dd, J = 13.6 Hz, J = 10.0 Hz); 1.99 (1H, dd, J = 13.5 Hz, J = 3.7 Hz); 1.75 (3H, s); 1.69 (1H, m); 1.39 (2H, m); 0.94, 0.92 (18H, 2s); 0.18, 0.15, 0.11, 0.10 (12H, 4s). ^{13}C NMR ($CDCl_3$): δ 142.6; 113.4; 67.7; 66.2; 65.5; 58.6; 55.1; 43.4; 39.6; 25.8; 23.9, 22.1; 18.0; −4.4, −4.8, −5.0. FT-IR (KBr): 3547 (O−H). Anal. Calcd for $C_{23}H_{46}O_4Si_2$ (442.79167): C 62.39, H 10.47. Found: C 62.43, H 10.26.

1-[(1*R*,2*S*,3*R*,4*S*,5*R*)-2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexyl]-3-methyl-3-buten-1-one (15). To a solution of a mixture of **13** and **14** (0.090 g, 0.2 mmol) in CH_2Cl_2 (6 mL) at 0 °C were added periodinane (0.109 g, 0.26 mmol, 1.2 equiv) and pyridine (0.6 mL). The reaction mixture was stirred at rt until all the starting material had been consumed (30 min). The mixture was then diluted with ethyl ether and poured into saturated aqueous $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture was stirred to dissolve the solid, and the layers were separated. The ether layer was washed with saturated $NaHCO_3$ and with water. After extractions with ethyl ether, the organic layer was dried ($MgSO_4$) and concentrated. Purification by preparative TLC (AcOEt/hexane 1:9) gave 0.089 g (99%) of **15** that crystallized as white needles. $[\alpha]^{20}_D$ −7.4 (*c* 0.81, CH_2Cl_2). Mp 59−60 °C. ^{1}H NMR ($CDCl_3$): δ 4.93 (1H, s); 4.81 (1H, s); 4.24 (1H, broad s); 4.13 (1H, d, J = 9.5 Hz); 3.20−2.94 (5H, m); 1.74 (3H, s); 1.47−1.43 (2H, m); 0.94, 0.89 (18H, 2s); 0.15, 0.13, 0.12, 0.04 (12H, 4s). FT-IR (KBr): 1709 C=O, ketone); 1651 (C=C). Anal. Calcd for $C_{23}H_{44}O_4Si_2$ (440.77573): C 62.68, H 10.06. Found: C 62.63, H 10.33.

1-[(1*R*,2*S*,3*R*,4*S*,5*R*)-2,5-Bis[(*tert*-butyldimethylsilyl)oxy]-3,4-epoxycyclohexyl]-3-methyl-2-buten-1-one (16). A catalytic amount of DBN was added to a solution of **15** (0.061 g, 0.14 mmol) in CH_2Cl_2 (0.6 mL). After stirring at rt for about 6 h, water was added, the mixture was extracted with CH_2Cl_2, the organic layer was dried ($MgSO_4$), and the solvent was evaporated. The residue was purified by preparative TLC (AcOEt/hexane 1:9) to afford 0.060 g (99%) of **16** as a colorless oil. $[\alpha]^{20}_D$ −6.1 (*c* 1.22, CH_2Cl_2). ^{1}H NMR ($CDCl_3$): δ 6.06 (1H, s); 4.25 (1H, d, J = 2.2 Hz); 4.14 (1H, d, J = 9.5 Hz); 3.09 (1H, d, J = 3.5 Hz); 3.06 (1H, broad s); 2.85−2.76 (1H, m); 2.14 (3H, s); 1.89 (3H, s); 1.48-1.42 (2H, m); 0.92, 0.86 (18H, 2s); 0.13, 0.12, 0.11, 0.01 (12H, 4s). FT-IR (film): 1691 (C=O, α,β-unsat ketone); 1620 (C=C). Anal. Calcd for $C_{23}H_{44}O_4Si_2$ (440.77573): C 62.68, H 10.06. Found: C 62.81, H 10.16.

1-[(1*R*,2*S*,3*R*,4*S*,5*R*)-3,4-Epoxy-2,5-dihydroxycyclohexyl]-3-methyl-2-buten-1-one (1). To a solution of **16** (0.083 g, 0.2 mmol) in THF (2.1 mL) at rt, was added a catalytic quantity of water followed by Bu_4NF (0.122 g, 0.47 mmol, 2.5 equiv). The mixture was stirred at rt till all the starting material had been consumed. The solution was diluted with ethyl acetate, and water was added. After stirring for 5 min, the mixture was washed with saturated NaCl and extracted with ethyl acetate. The evaporation of the solvent gave a residue that was purified by preparative TLC (AcOEt) to yield **1** (0.037 g, 93%) as a very viscous colorless oil that foamed under vacuum; its ^{1}H NMR data were identical with those of the natural product.[2] $[\alpha]^{23}_D$ +57.3 (*c* 0.84, anhydrous $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 6.15 (1H, s); 4.38 (1H, broad s); 4.26 (1H, d, J = 9.2 Hz); 3.26 (1H, d, J = 3.1 Hz); 3.22 (1H, broad s); 2.95 (1H, broad s); 2.67 (1H, m); 2.33 (1H, broad s); 2.16 (3H, s); 1.92 (3H, s); 1.77 (1H, m); 1.51 (1H, m). FT-IR (film): 3412 (O-H); 1683 (C=O); 1616 (C=C). EIMS *m*/*z* (relative intensity) 213 (50), 212 (9), 127 (40), 94 (27), 83 (100). HRMS Calcd for $C_{11}H_{16}O_4$: 212.104859. Found: 212.10486.

Acknowledgment. We thank the Junta Nacional de Investigação Científica e Tecnológica for a grant (Praxis XXI/BD/4527/94) conceded to M.R.V.

Supporting Information Available: Specific rotations, ^{1}H and ^{13}C NMR data, FTIR, and in some cases combustion analyses for the compounds **19**−**25** (41 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9617326