Total Synthesis of (−)-Specionin

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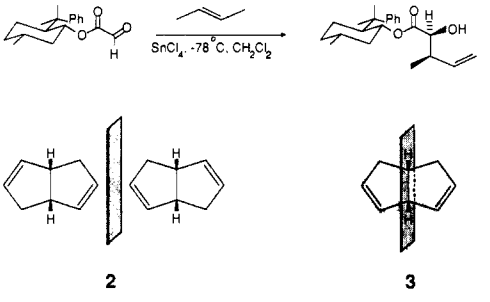
Abstract: The stereochemically discriminating, kinetic selection between the enantiotopically related alkene units in diene **3** was used to establish the absolute stereochemistry of the natural product specionin. Thus, reaction of **3** with glyoxylate **4*R*** afforded the ene adduct **5*S***. Dissection of the two-carbon glycolate unit added in the process provided the one external framework carbon in **1**. Further elaboration of **5*S*** involved straightforward functional group manipulation with excellent stereochemical component imparted by the bicyclo[3.3.0]octane framework and provided the natural product in optically pure form.

In 1982[1] we introduced the first practical ene reaction with control of absolute stereochemistry directed from Corey's chiral auxiliary 8-phenylmenthol.[2] In addition to the absolute stereochemical control observed in the formation of one or two new chiral centers in the process (Scheme I), the reaction was found to discriminate between alkene units related by mirror symmetry either in the kinetic selection between the enantiomeric pairs of a racemate (eq. **2**) or conversely between the π systems of a diene with internal mirror symmetry (eq. **3**). The former discrimination was used in our total synthesis of xylomollin[3] while we describe here our implementation of the latter process to the total synthesis of specionin (**1**) (Figure 1), a potent inhibitor of the feeding of the spruce bud worm.[4-6]

Direct implementation of our observations on the development of absolute stereochemistry in the ene reaction with diene **3** were initially hampered by the fact that the absolute sense of control imparted by the readily available enantiomer of 8-phenylmenthol[7] was the reverse of that required for the synthesis of the natural enantiomer of specionin.[8] Fortunately, we have uncovered an alternative and equally powerful auxiliary for these reactions in the form of *trans*-2-phenylcyclohexanol,[9] now readily available in both enantiomeric forms.[10] Thus, reaction of **3** with the *S* enantiomer of glyoxylate **4** provided adduct **5** that was demonstrated to have the opposite absolute stereochemistry at the bridgehead carbons of the bicyclo[3.3.0]octane framework (1*R*) as that from the reaction of **3** and the glyoxylate of (−)-8-phenylmenthol[11] (Figure 2). This was accomplished through comparison of the glycols **6** formed by reductive removal of the auxiliary from both of these ene adducts with lithium aluminum hydride.

Scheme I



2 **3**

Functional group manipulation of the glycol **6** derived from ene adduct **5*S*** (Figure 3) to that found in specionin required the following: (1) selective allylic oxidation of the alkene in the left-hand ring *with* double bond migration to form the exo, secondary alcohol and a trisubstituted alkene; (2) esterification of the resulting, secondary alcohol to form the *p*-hydroxybenzoate ester; (3) oxidation of the trisubstituted alkene formed in 1, above, to provide the exo epoxide in the left-hand ring; (4) oxidation of the remaining alkene in the right-hand ring to the dialdehyde and reconstitution to form the cyclic bis(acetal). The first process was accomplished in a selective fashion by taking advantage of the alcohol group in **8** as an appropriately positioned functionality to direct epoxidation only to the desired alkene, and both the primary alcohol and the inherent bias of the bicyclo[3.3.0]octane framework combine to direct oxidation to the exo face. Selective conversion of the primary alcohol to the aldehyde under Swern conditions[12] followed by treatment with mild base induced ring opening of the epoxide functionality to form the desired allylic alcohol. Transformation of the primary alcohol to the aldehyde also served to distinguish the primary and secondary alcohols of specionin so that the latter could be converted selectively to the aryl ester. This was accomplished by carbodiimide-induced coupling of the *p*-hydroxybenzoic acid protected from polymerization as the acetate. Reduction of the aldehyde with sodium borohydride in ethanol to re-form the primary alcohol afforded conditions sufficiently basic such that the acetate protecting group was removed. Final conversion of the ester **12** to specionin followed procedures used previously by this group to constitute the cyclic interplay between the aldehydes present in the iridoid terpenes.[3,13] Only one diastereomer (at C1 and C3) appeared to have been formed in this transformation, in contrast to previous synthetic efforts that involved formation of the cyclic, mixed bis(acetal) earlier in the synthetic sequence,[5] with different functionality present,[15] by different chemistry,[6] or under equilibrating condi-

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(2) Corey, E. J.; Ensley, H. E. *J. Am. Chem. Soc.* **1975**, *97*, 6908.

(3) Whitesell, J. K.; Minton, M. A. *J. Am. Chem. Soc.* **1986**, *108*, 6802.

(4) Chang, C. C.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1983**, 605.

(5) Racemic material was first prepared by Vandewalle who also published the first correct sturture for specionin. See: Van der Eycken, E.; Van der Eycken, J.; Vandewalle, M. *J. Chem. Soc., Chem. Commun.* **1985**, 1719. Van der Eycken, E.; De Bruyn, A.; Van der Eycken, J.; Callant, P.; Vandewalle, M. *Tetrahedron* **1986**, *42*, 5385.

(6) An alternative approach to the synthesis of optically active specionin has recently been communicated. See: Curran, D.; Jacobs, P. B.; Elliott, R. L.; Kim, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 5280. Kim, B. H.; Jacobs, P. B.; Elliott, R. L.; Curran, D. P. *Tetrahedron*, in press.

(7) See the discussion and references cited in: Whitesell, J. K.; Liu, C.-L.; Buchanan, C. B.; Chen, H.-H.; Minton, M. A. *J. Org. Chem.* **1986**, *51*, 551.

(8) Whitesell, J. K.; Allen, D. E. *J. Org. Chem.* **1985**, *50*, 3025.

(9) Whitesell, J. K.; Chen, H.-H.; Lawrence, R. M. *J. Org. Chem.* **1985**, *50*, 4663.

(10) Whitesell, J. K.; Lawrence, R. M. *J. Org. Chem.* **1986**, *51*, 4779.

(11) It should be noted that the enantiomers of the auxiliaries 8-phenylmenthol and *trans*-phenylcyclohexanol with the *same* three-dimensional orientation of groups afford *opposite* absolute stereochemical control in the ene reaction of the corresponding glyoxylates. The same observation has also been made in the ene reactions of the pyruvate esters: Whitesell, J. K.; Deyo, D., unpublished results.

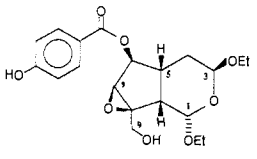
(12) Mancusco, A. J.; Swern, D. *Synthesis* **1981**, 165.

(13) Whitesell, J. K.; Matthews, R. S.; Minton, M. A.; Helbling, A. M. *J. Am. Chem. Soc.* **1981**, *103*, 3468.

(14) The rotation for natural specionin was $[\alpha]_D$ −30.7° (*c* 0.08, $CHCl_3$) and synthetic was $[\alpha]_D$ −29.5° (*c* 0.30, $CHCl_3$). Both observations were made by Curran.[6]

(15) Van der Eycken, E.; Janssens, A.; Vandewalle, M. *Tetrahedron Lett.* **1987**, *28*, 3519.

0002-7863/88/1510-3585$01.50/0



Specionin (1)

Figure 1.

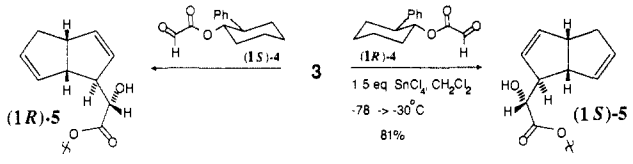


Figure 2.

tions.[15] It is possible that the mild conditions used here for the formation of the bis(acetal) system (pH 3) provided product that is representative of kinetic rather than thermodynamic control. Spectral details for synthetic material were identical with natural specionin in all respects except that the optical rotation was slightly higher than previously observed for either natural or synthetic samples.[14]

It should be noted that this synthesis represents a 10-operation sequence for the conversion of the readily available diene **3** (three steps from 1,5-cyclooctadiene) to specionin. The only conceptually nonessential steps were those required for the removal of the superfluous carbon added in the ene reaction and the oxidation and subsequent reduction of C9. The latter transformation was efficiently employed to simultaneously remove the acetate group used for protection of the phenolic hydroxyl during ester formation. Of primary significance is the application of stereochemical discrimination in the ene reaction that introduces absolute stereochemical bias in the desymmetrization of diene **3**, setting the two bridgehead carbons in the absolute sense found in specionin while simultaneously serving to introduce the single additional framework carbon required over the eight found in diene **3**.

Experimental Section

Reactions were routinely run under a dry nitrogen or argon atmosphere. Ether and tetrahydrofuran (THF) were freshly distilled from sodium benzophenone. Skelly-B (hexane) was stirred with concentrated sulfuric acid, neutralized with sodium carbonate, filtered through alumina, and distilled. Methylene chloride was distilled from CaH_2 and stored over molecular sieves prior to use. All other solvents and reagents were reagent grade and used as received unless stated otherwise. Brine refers to a saturated aqueous solution of sodium chloride. Organic solutions were dried over 4-Å molecular sieves before solvent removal on a rotary evaporator and high vacuum drying (for nonvolatile samples). HPLC separations were performed on normal-phase silica columns with refractive index detection with a Waters 6000A analytical pump or Prep 500 preparative system. IR spectra were run on Beckman Acculab 8 or Perkin-Elmer 298 infrared spectrophotometer as solutions in CH_2Cl_2. NMR spectra were obtained with Varian FT-80A, Varian EM390, Bruker WH-90, Varian HA-100, Nicolet NT-360, and General electric QE-300 and GN-500 spectrometers, in deuteriochloroform referenced to internal TMS unless otherwise noted. ^{13}C NMR assignments were confirmed by off-resonance decoupling where appropriate. Low-resolution mass spectra were obtained on a Bell and Howell Model 21-491 spectrometer and high-resolution mass spectra were obtained on a CEC 21-110B spectrometer. Only mass spectral peaks of m/z >100 and >10% relative intensity are reported.

trans*-2-Phenylcyclohexyl 2-Hydroxy-2-(*cis*-bicyclo[3.3.0]octa-3,7-dien-*exo*-2-yl)acetate (5*S*).** To a stirred solution of 8.69 g (82.0 mmol) of diene **3** and 19.0 g of *trans*-2-phenylcyclohexanol glyoxylate (182 mL of 0.45 M solution in methylene chloride, 82.0 mmol) in 1.3 L of methylene chloride at −78 °C was added dropwise 14.4 mL (1.5 equiv) of $SnCl_4$. The resulting solution was held at −30 °C for 19 h. The reaction was warmed to 0 °C and quenched by the addition of 200 mL of anhydrous ether. The solution was washed twice with water, and the aqueous portion was extracted with two 100-mL portions of methylene chloride. Standard isolation afforded 37.8 g of crude product, which was purified by HPLC (Prep 500, 9:1 Skelly-B–ethyl acetate) to yield 22.5 g (81%) of **5*S as a light yellow oil: $[\alpha]_D$ +77.8° (c 1.66, $CHCl_3$); ^1H NMR (360 MHz) δ 7.30–7.10 (m, 5 H, H on phenyl), 5.50 (m, 2 H, C3-H, C4-H, C7-H, or C8-H), 5.36 (m, 1 H, C3-H, C4-H, C7-H, or C8-H), 5.06 (ddd, 1 H, J = 11, 11, 5), 4.29 (ddd, 1 H, J = 6, 3, 3, C3-H, C4-H, C7-H, or C8-H), 3.98 (dd, 1 H, J = 9, 3, C9-H), 3.24 (dddd, 1 H, J = 9, 6, 3, 3, C5-H), 3.04 (m, 1 H, C1-H), 2.67 (ddd, 1 H, J = 12, 12, 4), 2.42 (dddd, 1 H, J = 17, 9, 5, 2, *endo*-C6-H), 2.34 (br d, 1 H, J = 9, H on OH), 2.20 (br s, 1 H, C2-H), 2.14 (m, 1 H), 2.03 (ddd, 1 H, 17, 2, 2, *exo*-C6-H), 1.90 (m, 2 H), 1.78 (m, 1 H), 1.61–1.30 (m, 4 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 173.2 (s, carbonyl C), 142.8 (s), 139.5 (d, C4), 133.7 (d, C8), 128.8 (d), 128.5 (d), 128.0 (d, C7), 127.4 (d), 126.8 (d), 124.9 (d, C3), 77.5 (d), 73.2 (d, C9), 54.3 (d, C2), 52.7 (t, C1), 50.0 (d), 47.6 (d, C5), 37.0 (t, C6), 34.0 (t), 32.4 (t), 25.7 (t), 24.7 (t); IR 3540, 2930, 2860, 1725, 1095, 1010 cm^{-1}; HRMS, m/e calcd for $C_{22}H_{26}O_3$ 338.1882, found 338.1873.

1-*cis*-Bicyclo[3.3.0]octa-3,7-dien-*exo*-2-yl-1,2-ethanediol (6). To a stirred solution of 0.39 g (10.2 mmol) of lithium aluminum hydride in 20 mL of dry THF was added dropwise 3.73 g (11.0 mmol) of **5*S*** in 16 mL of THF at a rate sufficient to maintain a gentle reflux, and the reaction mixture was stirred at room temperature for 19 h. The excess hydride was quenched by the careful addition of saturated aqueous sodium sulfate until foaming ceased, and solid sodium sulfate was added to take up the water. After the mixture was stirred for 0.5 h, the solids were removed by filtration and washed with ethyl acetate. The combined organics were concentrated, and the yellow oil was purified by column chromatography (silica gel), eluting first with 15:1 Skelly-B*nethyl* acetate to remove *trans*-2-phenylcyclohexanol (1.76 g, 91% recovery) and then

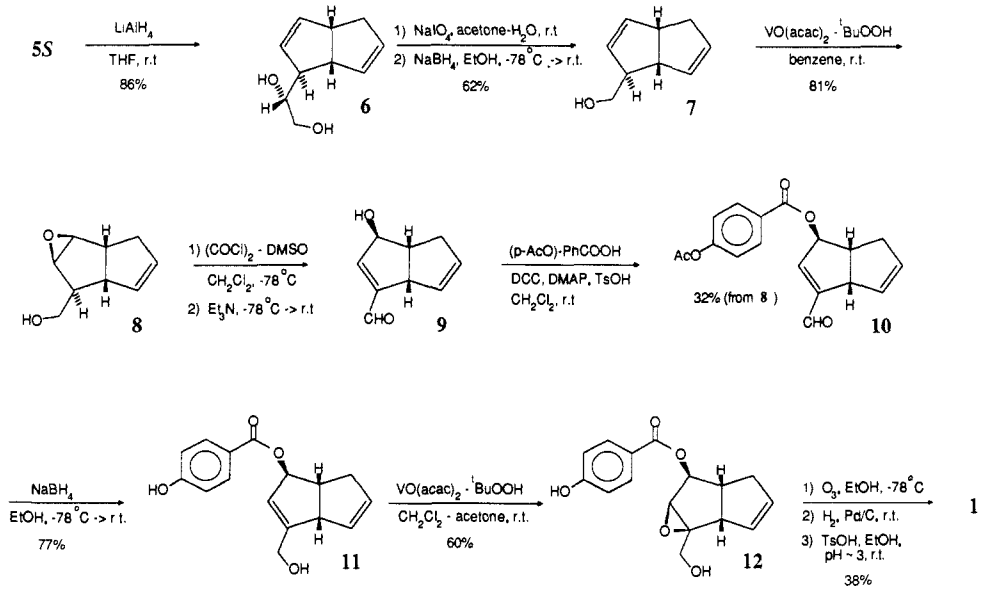


Figure 3.

with 1:1 Skelly-B–ethyl acetate, affording 1.57 g (86%) of the diol **6**: $[\alpha]_D$ +147.7° (*c* 1.18, $CHCl_3$); ^1H NMR (360 MHz) δ 5.73 (ddd, 1 H, *J* = 6, 2, 2, C4-H), 5.6 (m, 1 H, C3-H or C7-H), 5.56 (m, 2 H, C8-H and either C3-H or C7-H), 3.70 (m, 2 H, C9-H and C10-H), 3.5 (dd, 1 H, *J* = 12, 8, C10-H), 3.4 (dddd, 1 H, *J* = 12, 8, 5, 3, C5-H), 3.18 (m, 1 H, C1-H), 2.64 (m, 2H, C2-H), 2.55 (dddd, 1 H, *J* = 17, 9, 5, 2, *endo*-C6-H), 2.16 (ddd, 1 H, *J* = 17, 3, 3, *exo*-C6-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 137.9 (d, C4), 134.0 (d, C8), 128.4 (d, C3 or C7), 128.0 (d, C3 or C7), 75.9 (d, C9), 65.2 (t, C10), 54.1 (d, C2), 52.0 (d, C1), 47.4 (d, C5), 37.3 (t, C6); IR 3600–3300, 3030, 2920, 2850, 1100–1000 cm^{-1}; HRMS, *m/e* calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0991.

***cis*-Bicyclo[3.3.0]octa-3,7-dien-*exo*-2-ylmethanol (7).** To a stirred solution of 4.18 g (25.2 mmol) of diol **6** in 103 mL of acetone and 32 mL of water was added 10.8 g (50.4 mmol) of sodium periodate, and the reaction was stirred at room temperature for 19 h. Some of the resulting solids were dissolved by the addition of 20 mL of water, and the mixture was extracted with three 100-mL portions of methylene chloride. Standard workup gave 3.55 g of crude aldehyde, which was used without further purification.

The aldehyde was dissolved in 33 mL of absolute ethanol, and the solution was cooled to −78 °C under an inert atmosphere. After the addition of 1.0 g (26.4 mmol) of sodium borohydride, the reaction was stirred at −78 °C for 1 h and at room temperature for 22 h. The solvent was then removed in vacuo, the residue was taken up in methylene chloride, and the resulting solution was carefully acidified with 2 N HCl. The layers were separated, and the aqueous layer was extracted with three 25-mL portions of methylene chloride. Standard workup and purification by preparative HPLC (6:1 Skelly-B–ethyl acetate) provided 2.13 g (62% from **6**) or **7** as a colorless oil: $[\alpha]_D$ +150.9° (*c* 8.8, $CHCl_3$); ^1H NMR (360 MHz) δ 5.70 (ddd, 1 H, *J* = 5, 2, 2, C4-H), 5.57 (m, 3 H, C3-H, C7-H, C8-H), 3.61 (dd, 1 H, *J* = 11, 5, C9-H), 3.54 (dd, 1 H, *J* = 11, 6, C9-H), 3.42 (m, 1 H, C5-H), 3.18 (m, 1 H, C1-H), 2.70 (m, 1 H, C2-H), 2.55 (dddd, 1 H, *J* = 17, 9, 4, 3, *endo*-C6-H), 2.17 (ddd, 1 H, *J* = 17, 2, 2, *exo*-C6-H), 1.76 (s, 1 H, H on OH); ^{13}C NMR (20 MHz, $CDCl_3$) δ 137.6 (d, C4), 134.2 (d, C8), 128.9 (d, C3), 128.1 (d, C7), 66.3 (t, C9), 53.9 (d, C2), 52.1 (d, C1), 47.1 (d, C5), 37.3 (t, C6); IR 3600, 2910, 1025 cm^{-1}; HRMS, *m/e* calcd for $C_9H_{12}O$ 136.0888, found 136.0891.

***exo*-3,4-Epoxy-*cis*-bicyclo[3.3.0]oct-7-en-2-ylmethanol (8).** To a stirred solution of 2.13 g (15.6 mmol) of **7** in 128 mL of benzene at room temperature under a nitrogen atmosphere was added 0.042 g (1 mol%) of $VO(acac)_2$. The blue-green solution was treated with 8.5 mL (23.3 mmol) of a 2.74 M solution of *t*-BuOOH in benzene by dropwise addition (color became dark red), and the reaction mixture was stirred at room temperature for 24 h. The excess *t*-BuOOH was reduced by stirring the reaction mixture with a solution of 3.45 g of sodium sulfite in 10 mL of water for 2 h. The layers were separated, and the aqueous layer was extracted with two 50-mL portions of ethyl acetate. Standard workup and purification by column chromatography (silica gel, 4:1 Skelly-B–ethyl acetate) provided 1.93 g (81%) of **8** as a colorless oil: $[\alpha]_D$ +49.9° (*c* 11.3, $CHCl_3$); ^1H NMR (360 MHz) δ 5.69 (ddd, 1 H, *J* = 5, 5, 3, C7-H or C8-H), 5.60 (ddd, 1 H, *J* = 6, 5, 2, C7-H or C8-H), 3.81 (dd, 1 H, *J* = 10, 6, C9-H), 3.76 (dd, 1 H, *J* = 10, 7, C9-H), 3.65 (dd, 1 H, *J* = 3, 3, C4-H), 3.40 (d, 1 H, *J* = 3, C3-H), 3.10 (m, 1 H, C1-H), 2.61 (m, 2 H, C2-H and OH), 2.52 (dddd, 1 H, *J* = 18, 9, 2, 2, *endo*-C6-H), 2.22 (dddd, 1 H, *J* = 18, 6, 5, 3, *exo*-C6-H), 2.00 (dddd, 1 H, *J* = 8, 7, 7, 3, C5-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 133.5 (d, C8), 128.8 (d, C7), 63.0 (t, C9), 61.5 (d, C3 or C4), 61.3 (d, C3 or C4), 51.3 (d, C1), 50.4 (d, C2), 44.8 (d, C5), 33.9 (t, C6); IR 3600, 3020, 2910, 1035, 845 cm^{-1}; HRMS, *m/e* calcd for $C9H_{10}O$ (P–H_2O) 134.0732, found 134.0734; LRMS (CI) $[M + H]^+$ 153.

2-Formyl-*cis*-bicyclo[3.3.0]octa-2,7-dien-*exo*-4-yl 4-Acetoxybenzoate (10). To a stirred solution of 0.7 mL (8 mmol) of oxalyl chloride in 18 mL of methylene chloride under a nitrogen atmosphere at −78 °C was added dropwise 1.15 mL (16.2 mmol) of DMSO in 3.7 mL of methylene chloride. After 2 min 1.12 g (7.39 mmol) of alcohol **8** in 7.8 mL of methylene chloride was added dropwise, resulting in the formation of a white precipitate, and the reaction was stirred at −78 °C for 25 min. After the addition of 5.13 mL (38.8 mmol) of triethylamine, the reaction was stirred for an additional 5 min at −78 °C and then warmed to room temperature and stirred for 17 h. The reaction was quenched by the addition of 36 mL of water, and the layers were separated. The aqueous layer was extracted with two 30-mL portions of methylene chloride, and the combined organics were acidified with cold 2 N HCl and washed sequentially with saturated aqueous sodium bicarbonate and brine. After filtration through cotton, the solution was concentrated by distillation through a column packed with glass helices to give **9**. All of the product was used without further purification.

To a stirred solution of **9**, 1.6 g (8.9 mmol) of 4-acetoxybenzoic acid, 0.090 g (0.74 mmol) of 4-(dimethylamino)pyridine, and 0.14 g (0.74 mmol) of *p*-toluenesulfonic acid monohydrate in 70 mL of methylene chloride under a nitrogen atmosphere was added dropwise 2.4 g (12 mmol) of 1,3-dicyclohexylcarbodiimide in 38 mL of methylene chloride. A white precipitate formed within a few minutes, and the reaction was stirred at room temperature for 24 h. The solids were removed by filtration, and the resulting solution was concentrated. The residue was taken up in ethyl acetate, the undissolved solid was removed by filtration, and the solution was concentrated. The residue was then passed through a short silica gel column (1:1 Skelly-B–ethyl acetate) and purified by HPLC (Prep 500, 4:1 Skelly-B–ethyl acetate) to give 0.73 g (32% from **8**) of **10** as a colorless oil: $[\alpha]_D$ −122.0° (*c* 10.9, $CHCl_3$); ^1H NMR (360 MHz) δ 9.9 (s, 1 H, aldehydic H), 8.09 (d, 2 H, *J* = 8, C2′-H and C6′-H), 7.19 (d, 2 H, *J* = 8, C3′-H and C5′-H), 6.72 (br s, 1 H, C3-H), 5.84 (m, 2 H, C7-H and C8-H), 5.68 (dd, 1 H, *J* = 6, 3, C4-H), 4.17 (m, 1 H, C1-H), 3.11 (m, 1 H, C5-H), 2.83 (dd, 1 H, *J* = 17, 11, *endo*-C6-H), 2.55 (br d, 1 H, *J* = 17, *exo*-C6-H), 2.13 (s, 3 H, CH_3); ^{13}C NMR (20 MHz, $CDCl_3$) δ 189.7 (d, C9), 168.6 (s, carbonyl C), 165.3 (s, carbonyl C), 154.7 (s, C4′), 151.9 (d, C2), 145.0 (d, C3), 131.3 (d, C2′ and C6′), 130.6 (d, C7 or C8), 130.0 (d, C7 or C8), 127.5 (s, C1′), 121.8 (d, C3′ and C5′), 87.1 (d, C4), 54.7 (d, C1), 47.5 (d, C5), 37.6 (t, C6), 21.0 (q, CH_3 of acetate); IR 3050, 2920, 2820, 1760, 1715, 1685, 1600, 1365, 1195, 1155, 1110, 1095, 1015, 910, 855 cm^{-1}; HRMS, *m/e* calcd for $C_{18}H_{16}O_5$ 312.0998, found 312.1004.

2-(Hydroxymethyl)-*cis*-bicyclo[3.3.0]octa-2,7-dien-*exo*-4-yl 4-Hydroxybenzoate (11). To a stirred solution of 0.64 g (2.0 mmol) of **10** in 27 mL of absolute ethanol under a nitrogen atmosphere at −78 °C was added 0.077 g (2.0 mmol) of sodium borohydride in one solid portion. After 0.5 h at −78 °C, the reaction was warmed to room temperature and stirred for an additional 1 h. Th ethanol was removed in vacuo, and the residue was diluted with water and extracted with three 20-mL portions of ethyl acetate. The aqueous layer was saturated with NaCl and extracted with two 20-mL portions of ethyl acetate, and the combined organics were filtered through cotton and concentrated. Purification by semipreparative HPLC (μ Porasil, 1:1 Skelly-B–ethyl acetate) yielded 0.429 g (77%) of **11** as a white solid (mp 118–121 °C): $[\alpha]_D$ −149.3° (*c* 2.5, absolute EtOH); ^1H NMR (360 MHz) δ 7.90 (ddd, 2 H, *J* = 10, 2, 2, C2′-H and C6′-H), 6.95 (ddd, 2 H, *J* = 10, 2, 2, C3′-H and C5′-H), 5.84 (ddd, 1 H, *J* = 8, 3, 3, C7-H), 5.66 (m, 2 H, C3-H and C8-H), 5.55 (dd, 1 H, *J* = 5, 2, C4-H), 4.25 (s, 2 H, C9-H), 3.88 (m, 1 H, C1-H), 3.0 (m, 1 H, C5-H), 2.77 (dddd, 1 H, *J* = 17, 10, 5, 2, *endo*-C6-H), 2.46 (dddd, 1 H, *J* = 17, 4, 4, 2, *exo*-C6-H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 167.1 (s, carbonyl C), 161.0 (s, C4′), 153.4 (s, C2), 132.0 (d, C2′ and C6′), 130.5 (d, C7 or C8), 130.3 (d, C7 or C8), 122.5 (s, C1′), 122.2 (d, C3), 115.4 (d, C3′ and C5′), 87.7 (d, C4), 61.2 (t, C9), 57.4 (d, C1), 47.9 (d, C5), 37.8 (t, C6); IR 3540, 3400-3100, 3010, 2880, 1680, 1590, 1575, 1495, 1145, 1090, 1075, 830 cm^{-1}; HRMS; *m/e* calcd for $C_{16}H_{14}O_3$ (P – H_2O) 254.0943, found 254.0948; LRMS (CI) $[M + H]^+$ 273.

***endo*-2-(Hydroxymethyl)-*exo*-2,3-epoxy-*cis*-bicyclo[3.3.0]oct-7-en-*exo*-4-yl 4-Hydroxybenzoate (12).** Olefin **11** (0.22 g, 0.80 mmol) was dissolved in just enough reagent grade acetone to effect solution, and then 47 mL of dry CH_2Cl_2 was added. $VO(acac)_2$ (2.8 mg, 0.011 mmol) was added with good magnetic stirring (light blue color) followed by the addition of 0.45 mL (1.2 mmol) of 2.74 M *t*-BuOOH in benzene (which turned the solution dark red), and the reaction was stirred at room temperature for 22 h. The reaction was quenched by the addition of 5 mL of saturated aqueous sodium sulfite, and the mixture was stirred for 3 h. The layers were separated, and the aqueous layer was extracted with methylene chloride. Standard workup and purification by HPLC (one μ Porasil column, 1:2 Skelly-B–ethyl acetate) yielded 0.138 g (60%) of **12** as a white solid (mp 149–150 °C): ^1H NMR (500 MHz) δ 7.94 (ddd, 2 H, *J* = 9, 3, 3, C2′-H and C6′-H), 6.95 (ddd, 2 H, *J* = 9, 3, 3, C3′-H and C5′-H), 5.87 (m, 1 H, C7-H or C8-H), 5.82 (m, 1 H, C7-H or C8-H), 5.05 (dd, 1 H, *J* = 6, 3, C4-H), 4.10 (d, 1 H, *J* = 12, C9-H), 3.72 (d, 1 H, *J* = 12, C9-H), 3.65 (d, 1 H, *J* = 3, C3-H), 3.60 (m, 1 H, *endo*-C6-H), 3.0 (br s, 1 H, OH), 2.56 (m, 2 H, *exo*-C6-H, C1-H), 2.51 (m, 1 H, C5-H); ^{13}C NMR (125 MHz, acetone-d_6) δ 166.7 (s, carbonyl C), 162.8 (s, C4′), 133.0 (dd, C8), 132.6 (dd, C2′ and C5′), 130.1 (dd, C7), 122.3 (s, C1′), 116.1 (d, C3′ and C5′), 83.7 (d, C4), 69.8 (s, C2), 61.6 (d, C3), 61.4 (t, C9), 53.9 (d, C1), 43.4 (d, C5), 37.9 (t, C6); HRMS, *m/e* calcd for $C_{16}H_{16}O_5$ 288.0998, found 288.0992.

4-Hydroxybenzoic Acid 2,4-Diethoxyoctahydro-1a-(hydroxymethyl)-oxireno[4,5]cyclopenta[1,2-*c*]pyran-6-yl Ester (Specionin, 1). A solution of 0.052 g (0.18 mmol) of **12** in 35 mL of absolute ethanol was cooled to −78 °C under an argon atmosphere, and ozone was bubbled through until the solution turned blue. Nitrogen was passed through the solution to remove the excess ozone, and the mixture was slowly warmed to room temperature. After the addition of 0.036 g of 5% Pd/C, the ozonolysis product was catalytically reduced until the uptake of hydrogen ceased. The catalyst was removed by filtration through alumina, and the solvent was removed in vacuo. The reduction product was dissolved in 4 mL of

a solution of *p*-toluenesulfonic acid monohydrate in ethanol (0.011 g of $TsOH·H_2O$ in 20 mL of absolute ethanol, pH ~3), and the reaction mixture was stirred at room temperature for 23 h. The mixture was neutralized with saturated aqueous sodium bicarbonate and extracted with methylene chloride. The aqueous layer was extracted with two portions of methylene chloride, and the combined organics were filtered through cotton and concentrated. Separation by HPLC (μ porasil, 1:2 Skelly-B–ethyl acetate) yielded 0.026 g (38%) of **1** as a colorless oil: $[\alpha]_D$ −34.2° (*c* 0.26, $CHCl_3$); ^1H NMR (360 MHz) δ 7.90 (d, 2 H, *J* = 9, C2′-H and C6′-H), 6.85 (d, 2 H, *J* = 9, C3′-H and C5′-H), 5.33 (dd, 1 H, *J* = 8.5, 2, C6-H), 5.12 (d, 1 H, *J* = 5, C1-H), 4.9 (dd, 1 H, *J* = 7, 4, C3-H), 4.05 (d, 1 H, *J* = 13, C10-H), 3.85 (dq, 2 H, *J* = 17, 8, CH_2 on Et), 3.63 (d, 1 H, *J* = 2, C7-H), 3.55 (d, 1 H, *J* = 13, C10-H), 3.52 (m, 2 H, CH_2 on Et), 2.8 (dd, 1 H, *J* = 7, 4, C9-H), 2.35 (m, 1 H, C5-H), 1.95 (ddd, 1 H, *J* = 14, 5, 3, *endo*-C4-H), 1.83 (ddd, 1 H, *J* = 14, 7, 7, *exo*-C4-H), 1,26 (dd, 3 H, *J* = 7, 7, CH_3 on Et), 1.18 (dd, 3 H, *J* = 7, 7, CH_3 on Et); ^{13}C NMR (125 MHz, CD_3OD) δ 168.3 (s, carbonyl C), 163.7 (s, C4′), 133.0 (s, C2′ and C6′), 122.0 (s, C1′), 116.2 (s, C3′ and C5′), 97.8 (d, C1), 94.9 (d, C3), 80.7 (d, C6), 67.3 (s, C8), 64.8 (t, CH_2 of Et), 64.0 (t, CH_2 of Et), 61.4 (t, C10), 61.2 (d, C7), 41.2 (d, C9), 34.2 (d, C5), 30.3 (t, C4), 15.5 (q, CH_3 of Et), 15.5 (q, CH_3 of Et); IR 3580, 3500–3200, 2940, 2880, 1715, 1615, 1520, 1170, 1120, 1030, 980, 860 cm^{-1}; HRMS, *m/e* calcd for $C_{20}H_{26}O_8$ 394.1628, found 394.1636.

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Amphiphilic Reactions by Means of Exceptionally Bulky Organoaluminum Reagents. Rational Approach for Obtaining Unusual Equatorial, Anti-Cram, and 1,4 Selectivity in Carbonyl Alkylation

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Abstract: Exceptionally bulky, oxygenophilic organoaluminum reagents, methylaluminum bis(2,6-di-*tert*-butyl-4-alkylphenoxide) (MAD and MAT), have been successfully utilized for stereoselective activation of carbonyl moiety. Combination of MAD or MAT with carbon nucleophiles such as organolithiums or Grignard reagents generates a new amphiphilic reaction system in which the alkylation may be interpreted as the nucleophilic addition of a reactive organometallic compound to an electrophilically activated carbonyl substrate in order to account for the regio- and stereochemical consequences. In contrast to the ordinary alkylations, the amphiphilic alkylation disclosed herein would be categorized into the new, yet unexplored class of alkylation that exhibits high chemoselectivity to carbonyl compounds, and more significantly it allows excellent equatorial and anti-Cram selectivity in carbonyl alkylations, hitherto difficult by the existing methodologies. Further, unusual conjugate addition of organolithium reagents to α,β-unsaturated carbonyl compounds has been accomplished by using the amphiphilic reaction system.

Carbonyl alkylation has long been recognized to be one of the most important C–C bond formation in organic synthesis.[1] Particularly, interest has been focused on the diastereoselective addition of C-nucleophiles (organolithiums and Grignard reagents) to a carbonyl compound possessing at least one chiral center, resulting in what has been termed "1,*n*-asymmetric induction". Among these, the addition of C-nucleophiles to chiral α- or β-alkoxy aldehydes or ketones has been extensively studied in recent years.[2] Accordingly, two strategies (chelation and nonchelation control) have been developed which enabled the achievement of opposite sense of diastereoselectivity by appropriately choosing organometallic reagents. These methods have been successfully applied to a variety of natural product syntheses including ionophores, pheromones, and carbohydrates.[3] In contrast, the alkylation of ordinary chiral aldehydes and ketones having no ability to be chelated is governed only by the electronic and/or steric factors (nonchelation control), and the diastereochemical outcome would be predicted by the Cram rule.[4] Here the numerous studies so far have been pursued for achieving only one side of selectivity, i.e., axial selectivity for cyclic ketones and Cram selectivity for acyclic carbonyl compounds, and the corresponding equatorial and anti-Cram selectivity have not been realized for lack of appropriate methodologies. The objective of our study is the development of a rational approach to this problem which permits a high level of diastereofacial selectivity hitherto quite difficult by the existing methodologies.[5]

According to Ashby and other authors, the stereoselectivity of organometallic compound addition to cyclohexanones is considered to be influenced by two main factors: (1) the steric interaction of the incoming group with the 3,5-axial substituents and (2) the torsional strain of the incoming group with the 2,6-diaxial substituents.[1] For a cyclohexanone with no 3- or 5-axial substituent larger than hydrogen, the axial selectivity is obtainable by the use of bulky organometallics, since steric interaction of the entering, bulky reagent with the axial hydrogens outweighs torsional effects. For example, the axial selectivity is enhanced by changing the reagent from MeMgBr to EtMgBr, *i*-PrMgBr, and *t*-BuMgBr.[1] Similarly, $MeTi(O\text{-}i\text{-}Pr)_3$ possessing bulky ligands is much superior

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