4.53 (d, 1 H, J = 8.5 Hz), 5.53 (d, 1 H, J = 3.0 Hz), 6.27 (d, 1 H, J = 3.0 Hz).

***dl*-Ambrosin (1).** To 15 mg of synthetic damsin (0.072 mmol) in 3 mL of freshly distilled ethyl acetate was added 16 mg (0.079 mmol) of phenylselenenyl chloride at room temperature. Over a 4-h period, the reddish reaction mixture turned pale yellow, whereupon the reaction was quenched with solid sodium bicarbonate. The reaction was diluted with 50 mL of ethyl acetate, washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was evaporated under reduced pressure, leaving 47 mg of a residue. Purification on 10 g of silica gel (elution with ether–ethyl acetate 3:1) provided 24 mg (100%) of selenide **32**: R_f 0.92 (ether–ethyl acetate 3:1); IR ($CHCl_3$) 1765, 1732, 1660, 1580 cm^{-1}; NMR (CCl_4) δ 7.0–7.7 (m, 5 H), 6.15 (d, 1 H, J = 3 Hz), 5.35 (d, 1 H, J = 3 Hz), 3.45 (d, 1 H, J = 9 Hz).

To a solution of 24 mg (0.060 mmol) of the above monoselenide **32** in 1.5 mL of dry *tert*-butyl alcohol was added 35 mg (0.16 mmol) of sodium periodate at room temperature. The reaction mixture was warmed to 60 °C. After 2 h at 60 °C, the reaction was cooled to room temperature and diluted with 50 mL of ethyl acetate and 5 mL of brine. The aqueous layer was extracted with 2 × 15 mL portions of ethyl acetate, and the combined organic extracts were dried over anhydrous magnesium sulfate. The oily residue obtained upon evaporation of the solvent in vacuo was purified on 5 g of silica gel. Elution with ethyl acetate–benzene (1:1) afforded 7 mg (41%) of white crystalline *dl*-ambrosin (**1**): mp 188–190 °C (recrystallized from chloroform–hexane); IR ($CHCl_3$) 3025, 2985, 2960, 2940, 2880, 1770, 1710, 1665, 1595, 1478, 1458, 1410, 1386, 1370, 1345, 1330, 1315, 1305, 1285, 1275, 1245, 1214, 1160, 1115, 1105, 1085, 1068, 1024, 1010, 988, 970, 950, 835 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 1.06 (d, 3 H, J = 7 Hz), 1.18 (s, 3 H), 2.28 (m, 1 H), 2.55 (m, 1 H), 3.03 (m, 1 H), 3.47 (m, 1 H), 4.67 (d, 1 H, J = 9 Hz), 5.51 (d, 1 H, J = 3 Hz), 6.14 (dd, 1 H, J = 6 Hz and 3 Hz), 6.29 (d, 1 H, J = 3 Hz), 7.50 (dd, 1 H, J = 6 Hz and 2 Hz).

Acknowledgment. This investigation was supported by Public Health Service research grants (CA 13689 and CA 28865) from the National Cancer Institute and the National Institutes of Health NMR Facility for Biomedical Studies at Mellon Institute (RR-00292). We thank Drs. Mugio Nishizawa and Narihiko Fukamiya for many helpful discussions. We are indebted to Professor James A. Marshall for a sample gift of natural damsin and Professor Eloy Rodriguez for samples of natural ambrosin and damsin.

Registry No. (±)-**1**, 64813-79-2; (±)-**2**, 60133-11-1; (±)-**4**, 82041-93-8; dihydro-(±)-**4**, 82041-94-9; (±)-**7**, 82041-95-0; (±)-**9**, 64798-67-0; (±)-**10**, 82041-96-1; (±)-**11**, 82041-97-2; (±)-**11** alcohol, 81987-60-2; (±)-**16**, 81987-61-3; (±)-**18**, 82041-98-3; (±)-**18** monotosylate, 81987-62-4; (±)-**18** nitrile, 82041-99-4; (±)-**19**, 82042-00-0; (±)-**19** aldehyde, 81987-63-5; (±)-**19** alcohol, 81987-64-6; (±)-**20**, 82042-01-1; (±)-**20** monotosylate, 81987-65-7; (±)-**20** keto tosylate, 81987-66-8; (±)-**21**, 64798-77-2; (±)-**22**, 64798-78-3; (±)-**23**, 81987-67-9; (±)-**26**, 64798-79-4; (±)-**26** keto aldehyde, 81987-68-0; (±)-**27**a, 82042-02-2; (±)-**27**b, 82042-03-3; (±)-**28**, 64798-80-7; (±)-**29**, 64798-81-8; (±)-**30**, 64798-82-9; hydroxymethyl-**30**, 81987-69-1; **30** monomesylate, 81987-71-5; (±)-**31**, 64798-83-0; (±)-**32**, 81987-70-4; (±)-**8**, 54701-92-7; (±)-**12**, 82042-04-4; (±)-**13**, 82042-05-5; (±)-**14**, 81987-72-6; (±)-**15**, 81987-73-7; i, 81987-74-8; ii, 56029-64-2; 1-bromo-3-methyl-2-butene, 870-63-3.

Pseudoguaianolides. 2. Stereocontrolled Total Synthesis of the Helenanolide *dl*-Helenalin†,[1]

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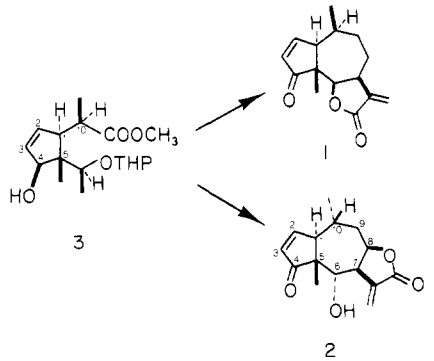
Received December 21, 1981

Abstract: A stereocontrolled total synthesis of the sesquiterpene lactone *dl*-helenalin (**2**) is described. The synthesis starts with cyclopentenol **3** and proceeds via the intermediacy of perhydroazulenone **20**. Elaboration of **20** into epoxy alcohol **28** sets the stage for introduction of the C(7)–C(8) cis-fused α-methylene-γ-butyrolactone. Oxidation at C(4) completes the synthesis of *dl*-helenalin.

Several years ago we embarked on a program that had as its ultimate goal the development of a general synthetic route for the construction of ambrosanolides (cf. ambrosin (**1**)) and helenanolides (cf. helenalin (**2**)) from a common synthetic intermediate. Our initial strategy centered around the key cyclopentenol **3**. The elaboration of **3** into ambrosin has been reported in the preceding paper.[2] We detail below the transformation of **3** into *dl*-helenalin, which constitutes the successful realization of our initial goal, i.e., the ability of cyclopentenol **3** to function as a *common synthetic* intermediate for both helenanolide and ambrosanolide synthesis.



Helenalin (**2**), which possesses six chiral centers about a flexible seven-membered ring, is representative of a group of pseudoguaianolides[3] known as helenanolides, which have as a characteristic feature a C(10) α-oriented methyl group. Helenalin was first isolated from *Helenium autumnale* over 65 years ago.[4] Its

* Address correspondence to this author at Indiana University.
† Dedicated to Professor Gilbert Stork on the occassion of his 60th birthday.

(1) Taken in part from the Ph.D. Thesis of George F. Majetich, University of Pittsburgh, 1979. For a preliminary account of this work, see: Ohfune, Y.; Grieco, P. A.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946.

(2) Grieco, P. A.; Majetich, G. F.; Ohfune, Y. *J. Am. Chem. Soc.*, preceding paper in this issue.

(3) Devon, T. K.; Scott, A. I. "Handbook of Naturally Occurring Compounds"; Academic Press: New York, 1972; Vol. II, pp 120–125. Šorm, F.; Dolejš, L. "Guaianolides and Germacranolides"; Holden-Day: San Francisco, 1965. Yoshioka, H.; Mabry, T. J.; Timmermann, B. W. "Sesquiterpene Lactones"; University of Tokyo Press: Tokyo, 1973. Romo, J.; Romo de Vivar, A. *Fortschr. Chem. Org. Naturst.* **1973**, *25*, 190. Fischer, N. H.; Olivier, E. J.; Fischer, H. D. *Ibid.* **1979**, *38*, 47.

(4) Reeb, *J. Pharm. Elsas. Lothringen* **1910**, *37*, 149. Lamson, P. D. *J. Pharmacol. Expl. Ther.* **1913**, *4*, 471. Clark, E. P. *J. Am. Chem. Soc.* **1936**, *58*, 1982.

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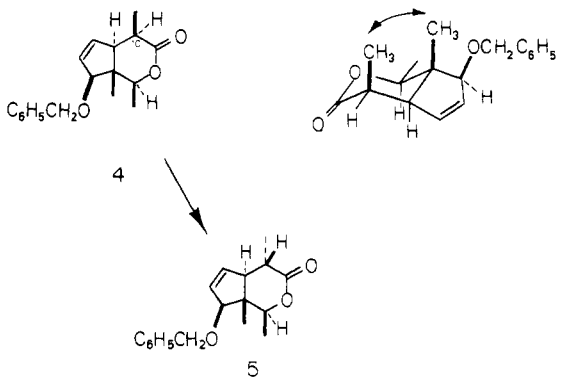
relative and absolute configuration, however, were not to be established until the early sixties.[5] Despite numerous attempts at hydroazulene synthesis over the past 20 years,[6] no member of the helenanolide family of pseudoguaianolides had been synthesized prior to the completion of the present investigation. Helenalin has also received considerable attention during the past decade because of its potent cytotoxic activity.[7] In contrast to the lack of progress in the helenanolide area, several reports have appeared in the literature during the past 5 years describing total syntheses of ambrosanolides (e.g., ambrosin,[8] confertin,[9] damsin,[8,9d,10] hymenin,[11a] parthenin,[11a] hysterin,[11b] and stramonin-B[11c]), which have as the characteristic feature a C(10) β-oriented methyl group. In developing a route to the helenanolides[13] from intermediate **3**, we set as a precondition the requirement that elaboration of the chirality located on the flexible hydroazulene ring system be achieved with complete stereochemical control. We detail below the results of our studies, which culminated in a completely stereocontrolled total synthesis of *dl*-helenalin.

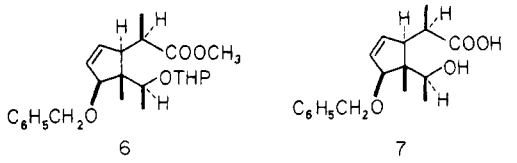
Results

Inversion of Configuration at C(10) and Synthesis of Perhydroazulenone 9. The utilization of cyclopentenol **3** as a key intermediate in any helenanolide synthesis requires that an efficient mechanism be available for the inversion of configuration at C(10).



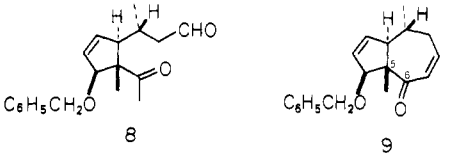
The requirement for inverting C(10) was made possible by the fact that the C(10) methyl group is adjacent to a carbomethoxy function. The projected scheme for carrying out this inversion with complete stereochemical control involved transformation of **3** into protected δ-lactone **4**. Examination of **4** reveals a severe 1,3-diaxial methyl,methyl interaction that we anticipated would be readily alleviated upon treatment with base, thus bringing about the requisite inversion of configuration at C(10) (cf. **4** → **5**).

We initiated this critical series of experiments by attempting to synthesize lactone **4**. The preparation of benzyl ether **6** from **3**[2] necessitated the use of tetra-*n*-butylammonium iodide in addition to sodium hydride in tetrahydrofuran containing benzyl bromide and hexamethylphosphoramide.[14] This is not surprising in view of severe steric crowding about C(4). Cleavage of the tetrahydropyranyl ether in **6** and subsequent hydrolysis of the methyl ester provided hydroxy carboxylic acid **7**. It was not

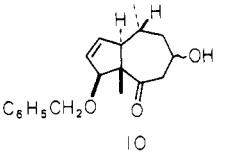


surprising to find that attempted lactonization of **7** with *p*-toluenesulfonic acid in benzene was unsuccessful; however, use of 1.3 equiv of *p*-toluenesulfonyl chloride in toluene containing 1,5-diazabicyclo[5.4.0]undec-5-ene at an elevated temperature gave exclusively a 70% yield of lactone **5** in which complete isomerization of the methyl group to the more stable equatorial position had occurred. That the equilibration took place after lactonization was demonstrated by carrying out the reaction at 0 °C, whereupon unequilibated lactone **4** could be isolated.

Having achieved the proper orientation of the C(10) methyl group, we focused our attention on construction of hydroazulenone **9**, which represents a logical precursor to *dl*-helenalin. The enone unit present in **9** was to function as the handle for the elaboration of the remaining three contiguous chiral centers on the seven-membered ring. We thus proceeded by converting lactone **5** into keto aldehyde **8**. This was accomplished via a four-step sequence



of reactions. Reduction of **5** with diisobutylaluminum hydride provided the corresponding lactol, which upon condensation with methoxymethylenetriphenylphosphorane (generated in benzene with sodium *tert*-amylate) and subsequent Collins oxidation and acid hydrolysis of the enol ether generated keto aldehyde **8**. Intramolecular aldol condensation with 1.5% potassium hydroxide in methanol gave in near-quantitative yield aldol **10**, which underwent β elimination in ca. 60% yield upon treatment with *p*-toluenesulfonic acid in benzene. Alternatively, crude aldol **10** could be transformed into its corresponding mesylate and treated with DBU, giving rise to enone **9** in ca. 65% overall yield. Hydrogenation of enone **9** afforded ketone **11** [NMR (CCl_4) δ 1.20 (s, 3 H), 0.85 (d, 3 H)], which was shown to be different from ketone **12** [NMR (CCl_4) δ 1.18 (s, 3 H), 1.02 (d, 3 H)] prepared previously[2] in connection with the total synthesis of ambrosanolides.



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(12) For a detailed conformational analysis of the hydroazulene system, see: De Clercq, P. J. *J. Org. Chem.* **1981**, *46*, 667.

(13) For recent syntheses of helenanolides, see: (a) Ohfune, Y.; Grieco, P. A.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1978**, *100*, 5946 (*dl*-helenalin). (b) Grieco, P. A.; Ohfune, Y.; Majetich, G. *J. Org. Chem.* **1979**, *44*, 3092 (*dl*-bigelovin). (c) *Tetrahedron Lett.* **1979**, 3265 (*dl*-mexicanin I). (d) Vandewalle, M.; Kok, P.; De Clercq, P. *J. Org. Chem.* **1979**, *44*, 4553 (*dl*-carpesiolin). (e) Roberts, M. R.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1979**, *101*, 7626 (*dl*-helenalin). (f) Lansbury, P. T.; Hangauer, D. G., Jr.; Vacca, J. P. *Ibid.* **1980**, *102*, 3964 (*dl*-aromatin, *dl*-aromaticin). (g) Ziegler, F. E.; Fang, J.-M. *J. Org. Chem.* **1981**, *46*, 827 (*dl*-aromatin).

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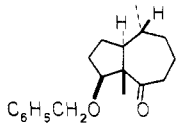

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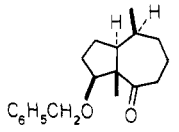

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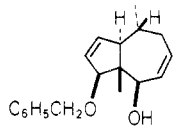
Attempts To Employ Enone 9 Directly in a Synthesis of *dl*-Helenalin. The original projected scheme for the preparation of helenalin featured reduction of the C(6) carbonyl in **9** from the side opposite the bulky C(5) methyl group (cf. allylic alcohol **13**) followed by an allylic 1,3 transposition (**13** → **15**) via reductive elimination of epoxy mesylate **14** (R = SO_2CH_3).[15] A direct



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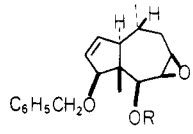

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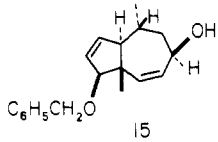

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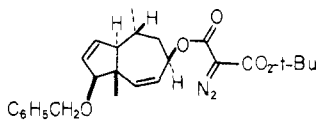
consequence of reducing the C(6) keto function in **9** is to produce the wrong configuration at C(6) relative to helenalin. However, epoxidation of **13** via assistance from the C(6) hydroxyl[16] provides **14** (R = H), which when properly derivatized and subjected to reductive elimination was expected to give rise to the proper configuration at C(8). Once **15** was secured, it was anticipated that the corresponding diazomalonate **16** would give way to the



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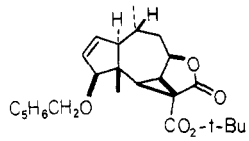

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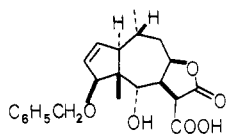
olefin addition product **17**.[17] Subsequent solvolytic ring opening of **17** would afford tricyclic lactone **18**, thus paving the way for completion of the synthesis of helenalin.



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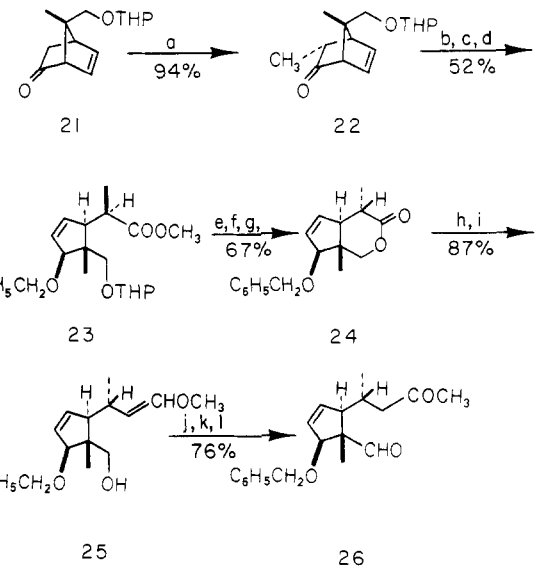
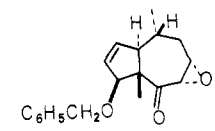
Reduction of hydroazulenone **9** with lithium aluminum hydride in tetrahydrofuran at −20 °C gave rise to a 91% yield of the crystalline alcohol **13**, mp 82–83 °C. Transition-metal-catalyzed epoxidation of allylic alcohol **11** with *tert*-butyl hydroperoxide in benzene containing vanadyl acetylacetonate provided none of the desired syn epoxy alcohol **14** (R = H). Much to our surprise a 60% yield of hydroazulenone **9** was isolated. We have since observed that transition-metal-catalyzed epoxidations of similar olefinic alcohols employing *tert*-butyl hydroperoxide give rise to enones.[18] In contrast, epoxidation of **13** with *m*-chloroperbenzoic acid in methylene chloride at 0 °C gave rise to a 78% yield of the crystalline syn epoxy alcohol **14** (R = H), mp 111–112 °C. Mesylation of **14** (R = H) proceeded smoothly; however, all our attempts to achieve a 1,3-allylic transposition via a reductive elimination have been unsuccessful.

Chart I. Construction of Keto Aldehyde **26**[a]



[a] (a) LDA, THF, 0 °C, MeI; (b) H_2O_2, OH^-, MeOH–HOH 1:1; (c) CH_2N_2; (d) NaH, THF, $PhCH_2Br$, HMPA, *n*-Bu_4NI, reflux; (e) MeOH, TsOH; (f) KOH, 30% aqueous EtOH; (g) TsCl, $PhCH_3$, DBU, 0 °C (15 mm) → reflux (3 h); (h) *i*-Bu_2AlH, $PhCH_3$, −78 °C; (i) Ph_3P=CHOMe, PhH; (j) 1 N HCl, THF; (k) MeLi, Et_2O, 0 °C; (l) PCC, NaOAc, CH_2Cl_2.

Unable to realize **15**, we turned our attention to the conversion of **9** into **20** via the Wharton rearrangement. Epoxidation of **9**



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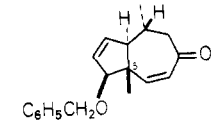

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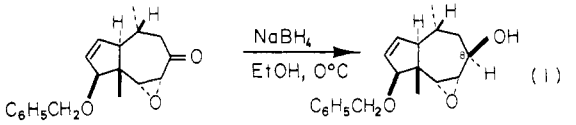
with *tert*-butyl hydroperoxide in tetrahydrofuran containing Triton B provided epoxy ketone **19**. Unfortunately, application and modification of the Wharton method were unsuccessful. We were therefore forced to abandon this approach.

Synthesis of Key Hydroazulene Intermediates for the Synthesis of Helenanolides. Undaunted by our inability to realize the formation of either **15** or **20** in acceptable yield, we returned to the aldol product **10** in an attempt to once again prepare enone **20**. Aldol **10**, without purification, was directly tetrahydropyranylated (TsOH, THP) at 0 °C in very high yield without any appreciable β elimination being detected. Subsequent reduction of the C(6) keto function followed by mesylation, cleavage of the tetrahydropyranyl ether, Jones oxidation, and β elimination (DBU) provided the desired perhydroazulenone **20**, mp 79–80 °C, from **10** in 60% overall yield.

Because of the unanticipated difficulties and the lengthy sequence of reactions required for the preparation of enone **9**, we turned our attention to the preparation of keto aldehyde **26** (Chart I), which represents a more logical precursor to **20**. The synthesis of **26** commences with the known bicyclo[2.2.1]heptenone **21**.[19] The conversion of **21** into keto aldehyde **26**, which proceeds via an efficient ten-step sequence of reactions, has been fully discussed on a previous occasion.[20] Subjection of keto aldehyde **26** to intramolecular aldol condensation with methanol–potssium hydroxide provided the intermediate aldol, which was smoothly dehydrated to hydroazulenone **20**, identical in all respects with the sample of **20** prepared by the circuitous route described above.

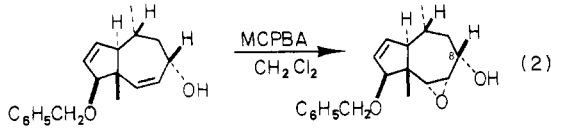
(15) Cf. Yasuda, A.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1976**, 2621. Marshall, J. A.; Ellison, R. H. *J. Am. Chem. Soc.* **1976**, *98*, 4312.
(16) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.
(17) Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361.
(18) Similar observations have been noted: Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.
(19) Grieco, P. A.; Pogonowski, C. S.; Burke, S. D.; Nishizawa, M.; Miyashita, M.; Masaki, Y.; Wang, C.-L. J.; Majetich, G. *J. Am. Chem. Soc.* **1977**, *99*, 4111.
(20) Grieco, P. A.; Ohfune, Y. *J. Org. Chem.* **1980**, *45*, 2251.

It was anticipated that during epoxidation of enone **20** with *tert*-butyl hydroperoxide–Triton B, the bulky *tert*-butyl hydroperoxide anion would approach the enone system from the side opposite the C(5) methyl group, giving rise to epoxy ketone **27**.



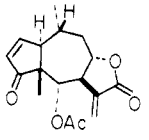
27 28

In fact, epoxidation of ***20*** *gave rise (93%) to a single crystalline epoxide* (***27***), mp 60–61 °C. Surprisingly, *reduction of epoxy ketone* ***27*** (eq 1) *provided exclusively in near quantitative yield, epoxy alcohol* ***28***, mp 90–91 °C. While we were not initially in a position to unambiguously assign structures to epoxide **27** and alcohol **28**, it became clear as a direct consequence of two additional remarkable experiments that our structural assignments were indeed correct. *Reduction of enone* ***20*** *with lithium aluminum hydride lead to the formation of a single allylic alcohol* ***29***, mp 62–64 °C, *which upon epoxidation (m-chloroperbenzoic acid) afforded a single epoxy alcohol* ***30***, mp 99–100 °C (eq 2).



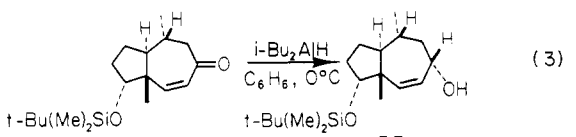
29 30

The absence of any epoxide formation at the C(2)–C(3) olefinic bond is not unexpected in view of the Henbest effect.[16] That the two alcohols **28** and **30** were isomeric at C(8) was demonstrated by oxidation (Collins) of each to the same crystalline epoxy ketone **27**. This information coupled with the expectation that in the case of **20** epoxidation occurred from the α face and that epoxidation of **29** took place also from the α face due to the C(8) α-hydroxyl strongly supported the above structural assignments. All of this was fully substantiated by the transformation of **28** into *dl*-helenalin and conversion of **30** into *dl*-bigelovin (**31**).[13b]



31

The stereospecificity observed in the transformation of **20** → **29** is not unique. Vandewalle and co-workers[13d] have shown that the reduction of enone **32** with diisobutylaluminum hydride gave rise exclusively to epimeric alcohol **33** (eq 3), in keeping with our



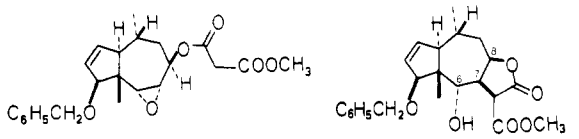
32 33

results. This suggests that profound differences exist in the conformational behavior of enones **20** and **32** compared to epoxy ketone **27**.[12,13d] Torsional constraints on the cycloheptenone ring system dictated by the presence of the *trans*-fused cyclopentene ring in the case of **20** are best accommodated by a twist-boat conformation **34** that still maintains π overlap in the enone system.

34 35

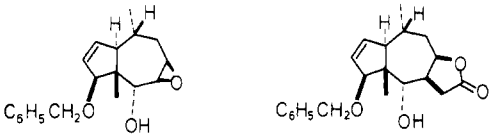
In the case of epoxide **27**, the torsional strain imposed on the system gives rise to the chair conformation **35**. Examination of **34** reveals that hydride attack should occur from the β face. In contrast, access to the ketone function from the β face in conformation **35** is severely hindered due to the C(5) methyl group and the C(10) proton.

Synthesis of *dl*-Helenalin. With the desired epoxy alcohol **28** available in sufficient quantity to pursue our synthetic studies toward helenalin, we prepared the malonate derivative **36** in order to study the intramolacular opening of the C(6)–C(7) α-epoxide. Successful epoxide opening to the tricyclic system **37** would complete the construction of all six chiral centers about the seven-membered ring. To date, all attempts to carry out the conversion of **36** into **37** have met with no success.



36 37

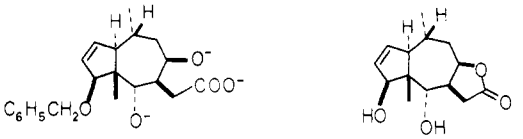
Disappointed by our failure to affect intramolecular opening of epoxide **36** with simultaneous construction of the C(7)–C(8) cis-fused γ-butyrolactone, we turned to a more conventional approach. We therefore set out to introduce the necessary two-carbon appendage at C(7) by examining the epoxide opening of **28** employing the dianion of acetic acid.[21] We were well aware of the potential for the alkoxide of epoxy alcohol **28** to rearrange to the alkoxide of the isomeric epoxy alcohol **38** during the course



38 39

of the reaction. Needless to say, such an event would have terminated this approach to helenalin. It was gratifying to discover that treatment of epoxide **28** with excess dilithioacetate in dimethoxyethane at 55 °C for 22 h resulted in the exclusive formation (ca. 60%) of tricyclic lactone **39**. After we arrived at intermediate **39**, the conclusion of the synthesis of helenalin seemed at first glance all but assured. Three seemingly simple operations remained: (a) debenzylation, (b) α-methylenation, and (c) oxidation at C(4).

Unfortunately, conditions normally employed for cleavage of benzyl ethers (hydrogenolysis or lithium–ammonia) were not compatible with the existing functionality in compound **39**. The sensitive γ-butyrolactone on the hydroazulene skeleton would require extensive protection: a process likely to entail several additional steps. However, the direct conversion of epoxy alcohol **28** into diol lactone **41** could, in principle, be accomplished by



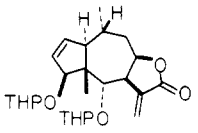
40 41

taking advantage of the intermediate trianion **40** generated during the course of opening epoxide **28** with dilithioacetate. To see if there was any validity to this surmise, we once again treated epoxide **28** with 14.7 equiv of dilithioacetate in dimethoxyethane at 55 °C for 22 h. The resultant trianion was added to a solution of lithium in liquid ammonia. After 1 min, the reaction was quenched with solid ammonium chloride. Workup with aqueous hydrochloric acid (pH 3) provided exclusively the crystalline tricyclic lactone **41**, mp 162–164 °C, in 86% overall yield. The direct conversion of epoxide **28** into **41** thus obviated the necessity

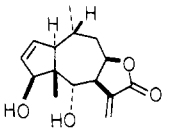
(21) Creger, P. L. *J. Org. Chem.* **1972**, *37*, 1907. Cf. Danishefsky, S.; Schuda, P. F.; Kitahara, T.; Etheredge, S. J. *J. Am. Chem. Soc.* **1977**, *99*, 6066.

of protecting the sensitive γ-butyrolactone ring. The structure of **41** was in accord with its observed 250-MHz ^{1}H NMR spectrum. The structure of tricyclic lactone **41** need not be debated, for this matter was unambiguously established by its transformation into *dl*-helenalin.

With the synthesis of **41** accomplished, we were ready to address α-methylenation and oxidation. α-Methylenation was performed[22] on the bis(tetrahydropyranyl) ether of **41** via the following sequence: (1) hydroxymethylation, (2) mesylation, and (3) β elimination with DBU in benzene. The overall yield of **42** for this process was 61%. Removal of the protecting groups with 60% aqueous acetic acid gave rise to a 78% yield of crystalline diol **43**, mp 157–158 °C.



42



43

The final transformation of diol **43** into *dl*-helenalin requires careful consideration in view of the known sensitivity of helenalin to both acids and bases.[23] Active manganese dioxide in *neutral* media was selected as the method of choice to accomplish the required allylic oxidation. Thus, oxidation of **43** with MnO_2 in 1:2 methylene chloride–benzene followed by chromatography on silicAR CC-7 provided in 65% yield pure crystalline *dl*-helenalin, mp 225–228 °C.

Synthetic helenalin was shown to be identical in all respects with an authentic sample of natural helenalin by comparison of spectral properties (IR, NMR, MS) and by its thin-layer mobility in several solvent systems.

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer, and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian T-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} = 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Ether, tetrahydrofuran, dimethoxyethane, and dioxane were distilled under argon from sodium metal with benzophenone ketyl as indicator. Dimethylformamide, hexamethylphosphoramide, dimethyl sulfoxide, pyridine, and benzene were distilled from calcium hydride. Methylene chloride was passed through a column of alumina prior to use.

Methyl α,5-Dimethyl-4-(phenylmethoxy)-5-[1-[(tetrahydro-2*H*-pyran-2-yl)oxy]ethyl]-2-cyclopentene-1-acetate (6). To a stirred suspension of 1.35 g (28.2 mmol) of 50% sodium hydride dispersion (washed with dry hexanes prior to use) in 60 mL of dry tetrahydrofuran cooled to 0 °C was added dropwise a solution of cyclopentenol **3** (5.87 g, 18.8 mmol) in 40 mL of tetrahydrofuran containing 3.32 g (18.8 mmol) of dry HMPA over a 30-min period. The reaction mixture was stirred at 0 °C for 30 min, warmed to room temperature, and stirred an additional 1 h. Freshly distilled benzyl bromide (4.82 g, 28.2 mmol) was added, followed by the addition of 2.78 g (7.53 mmol) of tetrabutylammonium iodide. The reaction was heated at 50 °C for 12 h, followed by cooling to room temperature. The reaction was quenched with a saturated aqueous solution of ammonium chloride. Removal of the solvent under reduced pressure afforded a residue which was taken up in 1 L of ethyl acetate and 50 mL of brine. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The crude material obtained was chromatographed on 400 g of silica gel (elution with hexanes–ether 2:1), providing 6.58 g (87%) of pure benzyl ether **6**: R_f 0.71 (hexanes–ether 1:1); IR (CCl_4) 3080, 3040, 2990, 2950, 2880, 2850, 1740, 1500, 1460, 1385, 1360, 1205, 1165, 1135, 1120, 1080, 1035, 995, 700 cm^{-1}; NMR (CCl_4) δ 7.26 (s, 5 H), 6.0–5.5 (m, 2 H), 4.50 (br s, 3 H), 4.1 (br s, 1 H), 3.9–3.2 (m, 6 H), 2.9–2.4 (m, 2 H), 1.8–0.6 (m, 15 H).

An analytical sample was prepared by distillation: 87–95 °C (bath temperature)/0.045 mmHg. Anal. Calcd for $C_{24}H_{34}O_5$: C, 71.61; H, 8.51. Found: C, 71.80; H, 8.52.

α,5-Dimethyl-4-(phenylmethoxy)-5-(1-hydroxyethyl)-2-cyclopentene-1-acetic Acid (7). A solution of 6.79 g (16.9 mmol) of tetrahydropyranyl ether **6** in 110 mL of absolute methanol was treated with 105 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of solid sodium bicarbonate. Removal of the solvent under reduced pressure (<0.1 mm) gave 5.47 g of an oily residue which was directly chromatographed on 200 g of silica gel. Elution with hexane–ether 2:1 gave 5.05 g (94%) of the corresponding hydroxy ester, which was used directly in the next reaction: R_f 0.44 (hexane–ether 2:1); an analytical sample was prepared by distillation, 101–104 °C (bath temperature/0.01 mmHg). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.86; H, 8.27.

A solution of 6.39 g (20.1 mmol) of the above ester in 60 mL of methanol containing 75 mL of a 10% aqueous potassium hydroxide solution was heated at 55 °C for 21 h. The solution was cooled and concentrated in vacuo. Water (100 mL) was added to the residue, and the resulting solution was extracted twice with 50-mL portions of ether. The aqueous solution was then acidified to pH 4 with 1.2 M hydrochloric acid at 0 °C. After the aqueous solution was exhaustively extracted with ethyl acetate, the ethyl acetate extracts were dried over anhydrous magnesium sulfate and filtered. The filtrate was concentrated, giving rise to 5.61 g of essentially pure crystalline hydroxy acid **7**: IR ($CHCl_3$) 3800–2500, 3000, 2950, 1705, 1500, 1465, 1380, 1360, 1080, 1060, 960, 920 cm^{-1}; NMR ($CDCl_3$) δ 7.30 (s, 5 H), 7.11 (br s, 2 H), 6.1–5.7 (m 2 H), 4.53 (br s, 2 H), 4.3–4.0 (m, 2 H), 2.9–2.4 (m 2 H), 1.5–0.9 (m 9 H). Recrystallization from hexanes–ether gave 5.44 g (89%) of analytically pure **7**, mp 102–103 °C. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.93; H, 7.99.

(1β,4β,4aα,7β,7aβ)-4,4a,7,7a-Tetrahydro-1,4,7a-trimethyl-7-(phenylmethoxy)cyclopenta[*c*]pyran-3(1*H*)-one (4). To a solution of 420 mg (2.20 mmol) of *p*-toluenesulfonyl chloride and 447 mg (1.47 mmol) of hydroxy acid **7** in 25 mL of dry toluene at 0 °C was added dropwise a solution of 670 mg (4.41 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 5 mL of toluene. The reaction mixture was stirred at 0 °C for 15 min and at ambient temperature for 1 h. The reaction was quenched by pouring the solution into a cold 10% aqueous hydrochloric acid solution. The product was isolated by extraction with 200 mL of ether. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo, leaving 947 mg of residue. The crude product was purified on 60 g of silica gel. Elution with 3:1 hexanes–ether provided 269 mg (64%) of lactone **4** as a crystalline solid: mp 87–88 °C; R_f 0.46 (hexanes–ether 1:1); IR ($CHCl_3$) 3080, 3000, 2950, 1720, 1500, 1470, 1460, 1390, 1200, 1050, 1030, 1000, 960 cm^{-1}; NMR (CCl_4) δ 7.3 (s, 5 H), 5.56 (br s, 2 H), 4.55 (AB q, 2 H, $\Delta\nu_{AB}$ = 7.2 Hz, J = 12 Hz), 4.1 (br s, 1 H), 2.9–2.6 (m, 2 H), 1.4–1.15 (m, 6 H), 0.9 (s, 3 H). Recrystallization from hexanes–ether gave analytically pure lactone **4**, mp 88–89 °C. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.69; H, 7.93.

(1β,4α,4aα,7β,7aβ)-4,4a,7,7a-Tetrahydro-1,4,7a-trimethyl-7-(phenylmethoxy)cyclopenta[*c*]pyran-3(1*H*)-one (5). A solution of 269 mg (0.94 mmol) of lactone **4** in 30 mL of toluene containing 214 mg (1.41 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene was refluxed. After 3 h, the reaction mixture was cooled and concentrated under high vacuum (0.1 mm). The residue was chromatographed on 40 g of silica gel. Elution with 2:1 hexanes–ether provided 246 mg (92%) of crystalline lactone **5**: mp 120–121 °C; R_f 0.77 (hexanes–ether 1:1); IR (CCl_4) 3080, 3040, 3000, 2940, 2870, 1735, 1500, 1455, 1390, 1350, 1310, 1190, 1180, 1160, 1060, 1030, 1005 cm^{-1}; NMR (250 MHz, CCl_4) δ 7.36–7.2 (m, 5 H), 5.96–5.88 (m, 1 H), 5.84–5.76 (m, 1 H), 4.58 (AB q, 2 H, $\Delta\nu_{AB}$ = 34.0 Hz, J = 12.2 Hz), 4.53 (q, 1 H, J = 7.2 Hz), 4.19 (br s, 1 H), 2.50 (m, 1 H), 2.40 (m, 1 H), 1.30 (d, 3 H, J = 7 Hz), 1.34 (d, 3 H, J = 7 Hz), 0.87 (s, 3 H). Recrystallization from ether provided analytically pure **5**, mp 121–122 °C. Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.50; H, 7.74. Found: C, 75.64; H, 7.82.

(1β,4α,4aα,7β,7aβ)-4,4a,7,7a-Tetrahydro-1,4,7a-trimethyl-7-(phenylmethoxy)cyclopenta[*c*]pyran-3[1*H*]-one (5) (One-Pot Procedure). To a solution of 3.78 g (19.8 mmol) of *p*-toluenesulfonyl chloride and 4.64 g (15.26 mmol) of hydroxy acid **7** in 175 mL of toluene at 0 °C was added dropwise a solution of 6.95 g (45.7 mmol) of 1,5-diazabicyclo-[5.4.0]undec-5-ene in 25 mL of toluene. The reaction mixture was allowed to warm to room temperature and stirred at ambient temperature for 1 h. The reaction was then brought to reflux. After 8 h, the reaction was cooled and 6.95 g (45.7 mmol) of additional DBU was added. Refluxing was continued for 8 h. After cooling to room temperature, the

(22) Grieco, P. A.; Hiroi, K. *J. Chem. Soc., Chem. Commun.* **1972**, 1317.
(23) Adams, R.; Herz, W. *J. Am. Chem. Soc.* **1949**, *71*, 2546, 2551, 2554.

solvent was removed under reduced pressure, and the residue was directly chromatographed on 150 g of silica gel. Elution with 2:1 hexanes–ether provided 3.05 g (70.5%) of lactone **5**, mp 121–122 °C, identical in all respects with the sample of **5** prepared above.

[1α,2β(S*),5β]-1-[2-(2-Formyl-1-methylethyl)-1-methyl-5-(phenylmethoxy)cyclopent-3-enyl]ethanone (8). To a solution of 1.60 g (5.59 mmol) of lactone **5** in 40 mL of dry toluene cooled to −78 °C was added dropwise 7.3 mL (7.3 mmol) of a 1 M solution of diisobutylaluminum hydride in toluene. After 30 min, the reaction was quenched at −78 °C by the careful addition of a saturated aqueous ammonium chloride solution. The product was isolated by extraction with ether. The organic layer was dried over anhydrous magnesium sulfate and the solvent was concentrated under reduced pressure. There was obtained 1.70 g of lactol, which was used directly in the next reaction.

To 7.56 g (22.0 mmol) of commercially available triphenyl(methoxymethyl)phosphonium chloride and 2.42 g (22.0 mmol) of sodium *tert*-amylate under nitrogen was added 60 mL of anhydrous benzene. Vigorous stirring at room temperature for 1 h produced (methoxymethylene)triphenylphosphorane (wine-red in color). A solution of 1.85 g (5.59 mmol) of the above lactol in 30 mL of dry benzene was added via syringe and allowed to stir at room temperature for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride and diluted with ethyl acetate and brine. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure. The crude enol ether was chromatographed on 300 g of silica gel. Elution with 2:1 hexanes–ether provided 1.53 g (87% overall from **5**) of enol ether as a mixture of cis and trans isomers, which were used directly in the next reaction; R_f 0.48 (hexanes–ether 1:1).

To a solution of 22.9 g (0.236 mol) of dry pyridine in 250 mL of dry methylene chloride at 0 °C was added 11.9 g (0.118 mol) of dry chromium trioxide. After an initial 30 min at 0 °C and 45 min at room temperature, the solution of Collins reagent was cooled to 0 °C, and a solution of 3.74 g (11.8 mmol) of the above enol ether in 50 mL of dry methylene chloride was added. After 30 min at 0 °C, the reaction was quenched with 700 mL of reagent grade ether. The residue that remained in the reaction vessel was taken up in water and extracted twice with 100-mL portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left a crude ketone, which was directly chromatographed on 200 g of silica gel. Elution with 1:1 hexanes–ether afforded 3.26 g (85%) of pure ketone, which was used directly in the next reaction: R_f 0.74 (hexanes–ether 1:1); IR (CCl_4) 1695 cm^{-1}; NMR (CCl_4) δ 2.08 (s, 3 H, CH_3CO).

A solution of 3.26 g (10.4 mmol) of the above enol ether in 100 mL of tetrahydrofuran containing 5 mL of a 10% aqueous hydrochloric acid solution was stirred at room temperature for 12 h. The reaction was quenched by the addition of solid sodium bicarbonate, and the solvent was removed under reduced pressure. Isolation of the product by ether extraction gave 3.15 g of essentially pure keto aldehyde **8**, which was chromatographed on 120 g of silica gel. Elution with 1:1 hexanes–ether yielded 3.08 g (99%) of pure keto aldehyde **8**: R_f 0.55 (hexanes–ether 1:1); IR ($CHCl_3$) 3070, 3030, 2980, 2930, 2870, 2810, 2710, 1725, 1700, 1500, 1460, 1450, 1355, 1300, 1220, 1085, 1025 cm^{-1}; NMR (250 MHz, CCl_4) δ 9.65 (s, 1 H), 7.25 (s, 5 H), 5.76 (s, 2 H), 4.50 (s, 1 H), 4.48 (AB q, 2 H, $\Delta\nu_{AB}$ = 18 Hz, J = 8.6 Hz), 2.86 (d, 1 H, J = 6.7 Hz), 2.4–2.05 (m, 6 H), 2.08 (s, 3 H), 1.20 (s, 3 H), 0.96 (d, 3 H, J = 7.0 Hz).

(3α,3aα,8β,8aβ)-3a,7,8,8a-Tetrahydro-3a,8-dimethyl-3-(phenylmethoxy)-4(3*H*)-azulenone (9). A solution of 2.87 g (9.58 mmol) of keto aldehyde **8** in 200 mL of a 1.5% absolute methanol–potassium hydroxide solution was stirred at room temperature for 8 h. The reaction was neutralized with saturated aqueous ammonium chloride solution. The methanol was removed under reduced pressure and the residue taken up with 300 mL of ether and 20 mL of brine. The aqueous layer was extracted with two 50-mL portions of ether, and the combined ether extracts were dried over anhydrous magnesium sulfate. Concentration of the solvent in vacuo provided 2.91 g of aldol **10**, which was used directly in the next reaction.

A cooled (0 °C) solution of 150 mg (0.47 mmol) of the above aldol **10** in 5 mL of dry methylene chloride containing 54 μL (0.70 mmol) of methanesulfonyl chloride and 97 μL of triethylamine was stirred at 0 °C for 3 min and room temperature for 3 h. The reaction was diluted with 100 mL of ether, washed with 10 mL of brine, and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent under reduced pressure afforded 121 mg of curde mesylate, which was used directly in the next reaction.

To the 121 mg of the above mesylate in 10 mL of dry benzene was added 106 mg (0.70 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene at room temperature. After 15 min the solvent was removed under reduced pressure, and the residue obtained was directly chromatographed on 10 g of silica gel (elution with hexanes–ether 2:1), providing 84 mg (64% overall from keto aldehyde) of pure enone **9**: R_f 0.77 (hexanes–ether 1:1); IR (CCl_4) 3080, 3030, 2980, 2940, 1665, 1500, 1455, 1400, 1350, 1310, 1265, 1140, 1110, 1090, 1075, 1030 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.37–7.12 (m, 5 H), 6.18 (ddd, 1 H, J = 12.6, 6.04, 4.39 Hz), 5.87 (ddd, 1 H, J = 12.63, 2.20, 1.65 Hz), 5.67–5.58 (m, 2 H), 4.83 (d, 1 H, J = 1.1 Hz), 4.66 (AB q 2 H, $\Delta\nu_{AB}$ = 23.5 Hz, J = 12 Hz), 2.63 (dtd, 1 H, J = 18.23, 5.85 Hz, $J_{w(coupling)}$ = 1.65 Hz), 2.44 (d, 1 H, J = 10.43 Hz), 2.20 (m, 1 H), 2.14–2.00 (m, 1 H), 1.14 (s, 3 H), 1.06 (d, 3 H, J = 7.14 Hz). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.60, H, 7.77.

(1α,3aβ,4β,8aα)-3a,4,5,8a-Tetrahydro-4,8a-dimethyl-1-(phenylmethoxy)-6(1*H*)-azulenone (20). A solution of 2.87 g (9.56 mmol) of aldol **10** in 50 mL of dry methylene chloride containing 30 mg of *p*-toluenesulfonic acid was cooled to 0 °C and treated with 1.03 g (12.3 mmol) of dihydropyran. After 1 h at 0 °C, the reaction was quenched with solid sodium bicarbonate solution, diluted with 300 mL of ether, and washed with 20 mL of brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, providing 4.06 g of crude THP. Chromatography on 200 g of silica gel (elution with hexanes–ether 1:1) provided 3.37 g (92% from keto aldehyde **8**) of the tetrahydropyranylated aldol as a mixture of diastereomers, which were used directly in the next reaction.

To a solution of 474 mg (1.23 mmol) of the above THF aldol in 25 mL of absolute methanol cooled to 0 °C was added portionwise 80 mg (2.16 mmol) of sodium borohydride. The reaction was stirred at 0 °C for 2 h and room temperature for 3 h. The reaction was quenched by the addition of water. The methanol was evaporated under reduced pressure and the residue taken up with 200 mL of ethyl acetate and 10 mL of brine. The aqueous phase was extracted twice with ethyl acetate, and the combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo provided 365 mg of pure alcohol, which was used directly in the next reaction.

To a solution of 365 mg of the above alcohol in 5 mL of dry pyridine cooled to 0 °C was added 150 mg (1.3 mmol) of methanesulfonyl chloride. The reaction was allowed to warm to room temperature. After 2 h, the reaction was quenched by pouring the solution into brine. The product was isolated by extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure afforded 419 mg (96%) of pure mesylate, which was used directly in the next reaction.

A solution of 419 mg (0.90 mmol) of the above mesylate in 15 mL of absolute methanol was treated at 0 °C with 10 mg of *p*-toluenesulfonic acid. The reaction mixture was stirred at 0 °C for 1 h and room temperature for 2 h. The reaction was quenched by the addition of solid sodium bicarbonate. Removal of the solvent under reduced pressure (<0.1 mm) gave 344 mg of hydroxy mesylate, which was employed directly in the next reaction.

A solution of 344 mg of the above alcohol in 15 mL of reagent grade acetone cooled to 0 °C was treated with standard Jones reagent until the red color persisted. After 15 min, the mixture was quenched with 2-propanol. The reaction was diluted with 30 mL of acetone. The acetone was decanted and evaporated, leaving an oily residue, which was dissolved in ethyl acetate. The chromium salts were dissolved in 50% brine and extracted twice with ethyl acetate. The combined ethyl acetate extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, leaving 342 mg of keto mesylate (R_f 0.31, hexanes–ether, 1:1), which was used directly in the next reaction.

To 342 mg (0.90 mmol) of the above keto mesylate in 15 mL of dry benzene was added 274 mg (1.8 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene. After 15 min at room temperature, the solvent was removed under reduced pressure, and the residue was directly chromatographed on 15 g of silica gel. Elution with 2:1 hexanes–ether afforded 200 mg (70% overall yield from keto aldehyde **8**) of enone **20** as a crystalline compound: mp 78–79 °C; R_f 0.53 (hexanes–ether 1:1); IR (CCl_4) 3070, 3025, 2970, 2940, 2900, 2870, 2825, 1670, 1605, 1458, 1385, 1368, 1348, 1305, 1260, 1230, 1215, 1168, 1140, 1085, 1055, 1030 cm^{-1}; NMR (250 MHz, CCl_4) δ 7.28 (br s, 5 H), 6.17 (AB q, 2 H, J = 11.5 Hz, $\Delta\nu_{AB}$ = 185.6 Hz, C(6) and C(7) olefinic protons), 5.77 (s, 2 H, C(2) and C(3) olefinic protons), 4.60 (AB q, 2 H, J = 12.1 Hz, $\Delta\nu_{AB}$ = 33.0 Hz, CH_2O), 4.52 (s, 1 H), 2.97 (dd, 1 H, J = 8.2, 12.1 Hz), 2.30–2.15 (m, 2 H), 2.01 (heptet, 1 H), 1.16 (s, 3 H), 1.13 (d, 3 H, J = 6.6 Hz). Recrystallization from hexanes–ether provided analytically pure enone, mp 79–80 °C. Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.88; H, 7.74.

(1aα,4β,4aβ,7α,7aα,7bα)-3,4,4a,7,7a,7b-Hexahydro-4,7a-dimethyl-7-(phenylmethoxy)azuleno[4,5-*b*]oxiren-2(1a*H*)-one (27). To a solution of 350 mg (1.24 mmol) of enone **20** in 12 mL of tetrahydrofuran was added 900 μL of Triton B (40% in methanol) followed by 900 μL of

tert-butyl hydroperoxide (70% in water). After 2 h at room temperature, the reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The mixture was poured into brine and extracted with ether. The aqueous layer was extracted several times with ether, and the combined ether extracts were washed with brine and dried over anhydrous magnesium sulfate. Filtration and evaporation provided 391 mg of crude epoxide, which was purified on 20 g of silica gel. Elution with 2:1 hexanes–ether provided 320 mg (87%) of crystalline epoxy ketone **27**: R_f 0.79 (hexane–ether 1:1); IR ($CHCl_3$) 3080, 3000, 2980, 2930, 2870, 1690, 1500, 1455, 1410, 1380, 1350, 1290, 1265, 1160, 1130, 1105, 1065, 1040, 1030, 960 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.26 (s, 5 H), 5.87–5.66 (m, 2 H), 4.63 (AB q, 2 H, $\Delta\nu_{AB}$ = 29 Hz, J = 12.09 Hz), 4.57 (s, 1 H), 3.33 (ABX, 2 H, $\Delta\nu_{AB}$ = 9.18 Hz, J_{ab} = 5.4 Hz, J_{ax} = 1.08 Hz), 2.63 (dd, 1 H, J = 11, 1.6 Hz), 2.43 (t, 1 H, J = 11.95 Hz), 2.17 (ddd, 1 H, J = 11.46, 3.24, 1.08 Hz), 1.75–1.59 (m, 1 H), 1.08 (d, 3 H, J = 8.97 Hz), 0.82 (s, 3 H). Recrystallization from hexanes provided analytically pure **27**, mp 60–61 °C. Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.76; H, 7.60.

(1aα,2aα,4β,4aβ,7α,7aα,7bα)-1a,2,3,4,4a,7,7a,7b-Octahydro-4,7a-dimethyl-7-(phenylmethoxy)azuleno[4,5-*b*]oxiren-2-ol (28). To a solution of 155 mg (0.52 mmol) of epoxy ketone **27** dissolved in 10 mL of absolute ethanol (cooled to 0 °C) was added 39 mg (1.04 mmol) of sodium borohydride in small quantities. The mixture was stirred at 0 °C for 1 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride and evaporated under reduced pressure. The residue was taken up in 100 mL of ethyl acetate and 5 mL of brine. The aqueous phase was extracted twice with 20-mL portions of ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo, and 240 mg of crude product was obtained. Chromatography on 15 g of silica gel (elution with hexanes–ether 1:1) provided 152 mg (98%) of pure crystalline **28**: mp 89–90 °C; R_f 0.43 (hexanes–ether 1:1); IR (CCl_4) 3630, 3600–3200, 3070, 3040, 2980, 2870, 1500, 1470, 1455, 1385, 1350, 1305, 1280, 1260, 1160, 1150, 1090, 1075, 1060, 1040, 1030, 1000, 900 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.28–7.11 (m, 5 H), 5.68–5.56 (m, 2 H), 4.66 (AB q, 2 H, $\Delta\nu_{AB}$ = 13.5 Hz, J = 12.8 Hz), 4.50 (s, 1 H), 4.20 (dt, 1 H, J = 9.45, 2.75 Hz), 3.04 (AB_2, 2 H, $\Delta\nu_{AB}$ = 11.28 Hz, J_{ab} = 4.7 Hz, J_{ab} = 3.5 Hz, J_{bb} = 9 Hz), 1.6–2.1 (m, 4 H), 1.36 (ddd, 1 H, J = 13.5, 6.30, 2.16 Hz), 1.07 (s, 3 H), 0.99 (d, 3 H, J = 6.93 Hz). Recrystallization from ether–hexanes gave analytically pure epoxy alcohol **28**, mp 90–91 °C. Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.70; H, 8.09.

(3aβ,4β,4aα,5α,7aβ,8β,9aβ)-3a,4,4a,5,7a,8,9,9a-Octahydro-4-hydroxy-4a,8-dimethyl-5-(phenylmethoxy)azuleno[6,5-*b*]furan-2(3*H*)-one (39). To a solution of 620 μL (8.2 mmol) of freshly dried diisopropylamine in 3 mL of dry dimethoxyethane under nitrogen at −42 °C (dry ice/3-pentanone) was added 2.72 mL (4.1 mmol) of a 1.50 M solution of *n*-butyllithium in hexane over a 10-min period. The solution was stirred at −42 °C for 10 min, followed by addition of 120 μL (2.06 mmol) of thoroughly dried acetic acid (the acetic acid was first distilled from potassium permanganate and then boron triacetate) in 1 mL of dimethoxyethane. The suspension was heated to 43 °C with stirring and was maintained at that temperature for 90 min. A solution of 42 mg (0.14 mmol) of epoxy alcohol **28** in 0.8 mL of dimethoxyethane was added to the reaction mixture. The reaction mixture was stirred at 55 °C for 20 h. After cooling to 0 °C, 6 mL of water was added and the resulting solution extracted twice with 20-mL portions of ether. The combined ether layers were extracted with 10 mL of a 2% aqueous sodium hydroxide solution. The combined aqueous layers were acidified to pH 3 by 10% aqueous hydrochloric acid and extracted exhaustively with ethyl acetate. The solvent was removed under reduced pressure, leaving 55 mg of a residue that was dissolved in 50 mL of benzene containing a trace of *p*-toluenesulfonic acid in order to induce lactonization. After 15 min, evaporation of the benzene under reduced pressure provided 47 mg of crude tricyclic lactone **39**, which was purified on 10 g of silica gel. Elution with 1:3 hexanes–ether gave 3 mg of recovered starting material **28** (R_f 0.90, ether) and 28 mg (58%) of pure lactone **39**: R_f 0.65; IR (CCl_4) 3650–3200, 3070, 3040, 2960, 2940, 1785, 1470, 1455, 1350, 1200, 1185, 1140, 1085, 1025 cm^{-1}; NMR (250 MHz, CCl_4) δ 7.33–7.2 (m, 5 H), 5.72 (s, 2 H), 4.7–4.6 (m, 1 H), 4.55 (AB q, 2 H, $\Delta\nu_{AB}$ = 22.4 Hz, J = 11.2 Hz), 4.56 (d, 1 H, J = 2.64 Hz), 3.71 (d, 1 H, J = 11.2 Hz), 2.84 (br s, 1 H, OH), 2.79–2.57 (m, 3 H), 2.14 (d, 1 H, J = 10.9 Hz), 1.94–1.69 (m, 3 H), 1.08 (d, 3 H, J = 7.3 Hz), 1.06 (s, 3 H). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.79; H, 7.48.

(3aα,4α,4aβ,5β,7aα,8α,9aα)-3a,4,4a,5,7a,8,9,9a-Octahydro-4,5-dihydroxy-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (41). To a solution of 1.86 mL (12.0 mmol) of freshly distilled diisopropylamine in 10 mL of dry dimethoxyethane under nitrogen at −42 °C (dry ice/3-pentanone) was added 8.16 mL (11.8 mmol) of a 1.50 M solution of *n*-butyllithium in hexane over a 10-min period. The solution was stirred at −42 °C for 10 min, followed by the addition of 372 mg (360 μL, 5.6 mmol) of scrupulously dried acetic acid. The resultant suspension was heated at 43 °C for 90 min. A solution of 121 mg (0.4 mmol) of epoxy alcohol **28** in 30 mL of dimethoxyethane was added to the solution of dilithioacetate in dimethoxyethane. The reaction was stirred at 55 °C for 21 h. The reaction was cooled to room temperature and diluted with 10 mL of dimethoxyethane. The reaction mixture was transferred via a cannula (double-tipped stainless steel needle) by nitrogen pressure into a solution of 80 mL of ammonia containing 80 mg (11.4 mmol) of lithium metal. After stirring for 1 min, the reaction was quenched by the addition of solid ammonium chloride. The ammonia was removed under reduced pressure, and 5 mL of water were added. The resulting solution was acidified with 10% aqueous hydrochloric acid to pH 3 and was exhaustively extracted with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure left crude trihydroxy carboxylic acid, which was dissolved in 75 mL of benzene. The benzene was removed in vacuo in order to ensure complete lactonization. This process was repeated if lactonization was incomplete. A crude product (131 mg) was obtained, which was purified on 10 g of silica gel. Elution with ethyl acetate provided 88 mg (86%) of crystalline tricyclic lactone **41**: mp 161–162 °C; R_f 0.42 (ethyl acetate); IR ($CHCl_3$) 3600–3150, 3000, 2965, 2940, 1765, 1600, 1470, 1455, 1420, 1380, 1325, 1225, 1220, 1140, 1055, 1020, 970 cm^{-1}; NMR (250 MHz, CCl_4) δ 5.75–5.61 (m, 2 H), 4.91 (s, 1 H), 4.86–4.72 (m, 1 H), 3.78 (d, 1 H, J = 11.4 Hz), 3.37 (br s, 1 H, OH), 3.0–2.76 (m, 3 H), 2.55 (br s, 1 H, OH), 2.16 (d, 1 H, J = 11.2 Hz), 2.0–1.80 (m, 3 H), 1.11 (d, 3 H, J = 5.25 Hz), 1.10 (s, 3 H). Recrystallization from methylene chloride–ether provided analytically pure **41**, mp 162–164 °C. Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.99. Found: C, 66.41; H, 7.89.

(3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-Octahydro-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[6,5-*b*]furan-2(3*H*)-one. A solution of 28 mg (0.11 mmol) of lactone diol **41** in 4 mL of dry methylene chloride containing 1 mg of *p*-toluenesulfonic acid was cooled to 0 °C and treated with 40 μL (0.5 mmol) of dihydropyran. After 1 h at 0 °C and 1 h at room temperature, the reaction was quenched by the addition of solid sodium bicarbonate. The reaction mixture was diluted with 50 mL of ether and washed with 5 mL of brine. The organic layer was dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure, leaving 45 mg of a residue. Chromatography on 5 g of silica gel (elution with hexanes–ether 1:2) gave 39 mg (82%) of (3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-octahydro-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[6,5-*b*]furan-2(3*H*)-one as a crystalline substance: mp 37–40 °C; IR ($CHCl_3$) 1760 cm^{-1}. Recrystallization from ether provided analytically pure material, mp 38–40 °C. Anal. Calcd for $C_{24}H_{36}O_6$: C, 68.55; H, 8.63. Found: C, 68.27; H, 8.68.

(3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-Octahydro-4,5-dihydroxy-3-methylene-4a,8-dimethylazuleno[6,5-*b*]furan-2(3*H*)-one (43). To a solution of diisopropylamine (31 μL, 0.21 mmol) in 1 mL of dry tetrahydrofuran cooled to −78 °C was added 136 μL (0.21 mmol) of a 1.50 M solution of *n*-butyllithium in hexane. After 15 min, a solution of 62 mg (0.15 mmol) of (3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-octahydro-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[6,5-*b*]furan-2(3*H*)-one in 0.7 mL of dry tetrahydrofuran was added dropwise over a period of 30 min. After 30 min at −78 °C, the reaction was warmed to −25 °C and formaldehyde, generated from 200 mg of paraformaldehyde at 150 °C, was passed through the reaction mixture with the aid of a stream of dry nitrogen. After complete depolymerization, the reaction mixture was stirred for an additional 30 min at −25 °C. The reaction was quenched by the addition of a saturated aqueous solution of ammonium chloride. The reaction mixture was diluted with 30 mL of ethyl acetate, and the organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent under reduced pressure provided 67 mg of a residue which was purified on 10 g of silica gel. Elution with ether gave 28 mg of recovered starting lactone and 27 mg (75% based on recovered starting material) of (3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-octahydro-3-(hydroxymethyl)-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno-[6,5-*b*]furan-2(3*H*)-one, which was used directly in the next reaction; IR (CCl_4) 3630, 3600–3300, 1770 cm^{-1}.

A solution of the above hydroxymethylated lactone (84 mg, 0.187 mmol) in 3 mL of pyridine containing 24 μL (0.28 mmol) of methanesulfonyl chloride was stirred for 2 h at 0 °C. The reaction mixture was poured into 3 mL of water and repeatedly extracted with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, leaving 105 mg of essentially pure mesylate, which was used directly in the next reaction.

The above mesylate (105 mg, 0.187 mmol) was dissolved in 3 mL of dry benzene containing 50 μL of 1,5-diazabicyclo[5.4.0]undec-5-ene.

After 1 h at room temperature, the reaction was concentrated in vacuo, and the residue was chromatographed on 10 g of silica gel. Elution with 1:2 hexane–ether gave 70 mg (82%) of (3aα,4α,4aβ,5β,7aα,8a,9aα)-3a,4,4a,5,7a,8,9,9a-octahydro-3-methylene-4a,8-dimethyl-4,5-bis[(tetrahydro-2*H*-pyran-2-yl)oxy]azuleno[6,5-*b*]furan-2(3*H*)-one (**42**), which was used directly in the next reaction; IR (CCl_4) 1775, 1660 cm^{-1}.

A solution of 24 mg (0.053 mmol) of **42** in 0.7 mL of glacial acetic acid–water (60:40, v/v) was stirred at room temperature for 5 h. Removal of the solvent under reduced pressure (<0.1 mm) gave an oily residue, which was directly chromatographed on 5 g of silica gel. Elution with ether gave 12.9 mg (92% yield) of tricyclic α-methylene lactone **43** as a crystalline material: mp 155–157 °C; R_f 0.34 (ether); IR ($CHCl_3$) 3600–3200, 3000, 2970, 2930, 1760, 1660, 1470, 1455, 1405, 1380, 1370, 1350, 1320, 1305, 1280, 1260, 1230, 1160, 1110, 1050, 1005 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 6.36 (d, 1 H, *J* = 1.75 Hz), 5.87 (d, 1 H, *J* = 1.75 Hz), 5.76–5.66 (m, 2 H), 4.96 (s, 1 H), 4.84–4.74 (m, 1 H), 3.78 (d, 1 H, *J* = 10.95 Hz), 3.43–3.35 (m, 1 H), 2.80 (br s, 1 H, OH), 2.60 (br s, 1 H, OH), 2.22 (d, 1 H, *J* = 11.4 Hz), 2.00–1.75 (m, 3 H), 1.12 (d, 3 H, *J* = 6.78 Hz), 1.09 (s, 3 H). Recrystallizaiton from acetone–hexanes provided analytically pure **43**, mp 157–158 °C. Anal. Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.09; H, 7.58.

***dl*-Helenalin (2).** To a suspension of freshly prepared manganese dioxide (120 mg) in a mixture of dry methylene chloride (1.5 mL) and dry benzene (3.0 mL) was added 18 mg (0.040 mmol) of tricyclic alcohol **43**. After 2 h at room temperature, the mixture was diluted with 20 mL of ether and filtered. The solvent was removed under reduced pressure, and the residue was chromatographed on silicAR-CC7. Elution with ether provided 12 mg (65%) of *dl*-helenalin as a crystalline compound: mp 223–226 °C; R_f 0.51 (ether); IR ($CHCl_3$) 3600, 3550–3200, 3020, 2975, 2940, 1765, 1710, 1660, 1580, 1460, 1380, 1360, 1340, 1320, 1200, 1275, 1210, 1160, 1110, 1050, 980, 945 cm^{-1}; NMR (250 MHz, $CDCl_3$) δ 7.70 (dd, 1 H, *J* = 1.7, 6.0 Hz), 6.38 (d, 1 H, *J* = 3.1 Hz), 6.08 (dd, 1 H, *J* = 2.8, 5.9 Hz), 5.79 (d, 1 H, *J* = 3.1 Hz), 4.98 (td, 1 H, *J* = 8.9, 2.6 Hz), 4.46 (dd, 1 H, *J* = 1.7, 4.3 Hz), 3.56 (m, 1 H), 3.07 (dt, 1 H), 2.45 (d, 1 H, *J* = 4.3 Hz, OH), 2.28 (m, 1 H), 2.08 (m, 1 H), 1.80 (m, 1 H), 1.28 (d, 1 H, *J* = 7.5 Hz), 1.00 (s, 1 H). Recrystallization from acetone–hexane provided analytically pure *dl*-helenalin, mp 225–228 °C. Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92. Found: C, 68.60; H, 6.87.

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Registry No. 2, 68330-47-2; **3**, 82041-93-8; **4**, 71748-37-3; **5**, 82043-27-4; **5** lactal, 71686-31-2; **5** (*E*)-enol ether derivative, 82010-13-7; **5** (*Z*)-enol ether derivative, 82043-28-5; **5** crude ketone derivative, 68241-51-0; **6**, 82043-29-6; **7**, 82043-30-9; **7** methyl ester, 82010-14-8; **8**, 68241-52-1; **9**, 71686-32-3; **10**, 71686-33-4; **10** mesylate, 82010-15-9; **10** THP, 68241-53-2; **10** THP alcohol, 82010-16-0; **10** THP mesylate, 82010-17-1; **10** hydroxy mesylate, 82010-18-2; **10** keto mesylate, 82010-19-3; **20**, 68241-54-3; **27**, 68241-55-4; **28**, 68306-73-0; **39**, 82010-20-6; **41**, 68257-98-7; **41** bis(THP), 68241-56-5; **41** hydroxymethyl derivative bis(THP), 82010-21-7; **41** hydroxymethyl mesylate bis(THP), 82010-22-8; **42**, 82026-00-4; **43**, 68241-57-6; benzyl bromide, 100-39-0; (methoxymethylene)triphenylphosphorane, 20763-19-3.

Communications to the Editor

Mechanism of Arene Carbon–Hydrogen Bond Activation by $[C_5(CH_3)_5]Rh[P(CH_3)_3](H)(C_6H_5)$. Evidence for Arene Precoordination

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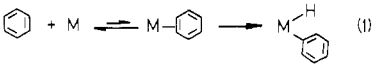
The activation of unreactive carbon–hydrogen bonds is one of the most interesting yet elusive problems challenging chemists today. While significant advances in carbon–hydrogen bond activation by soluble transition-metal complexes have appeared in the literature over the past few years, the great majority of these reports involve oxidative addition of the metal to arene C–H bonds.[1] Homogeneous activation of alkane C–H bonds has also been observed by several workers recently.[2] In addressing the problem of C–H bond activation, we decided first to investigate in detail the nature of the activation process. While many types of activation mechanisms have been established in other metal systems (such as electrophilic attack[3a] or free radical[3]), we chose here to study exclusively activation by oxidative addition, where greater control of selectivity might be accomplished by varying the properties of the metal complex.

The abundance of complexes that are capable of activating arenes but not alkanes is surprising in light of the difference in bond strengths involved (110 kcal/mol for benzene vs. ~95 kcal/mol for an alkane[4]) and suggests a kinetically higher reactivity for arenes. Parshall has proposed that arene coordination may precede oxidative addition of the C–H bond (eq 1), providing



(1)

an additional 5–10 kcal/mol of driving force through the $T\Delta S^{\ddagger}$ term in the $\Delta G^{\ddagger}$ for the oxidative addition,[5] although evidence for such an intermediate is lacking. This entropic contribution to $\Delta G^{\ddagger}$ also manifests itself in the many examples of intramolecular alkyl and aryl C–H bond activation.[1,6] We report here chemical evidence for the intermediacy of an η^2-arene complex in the activation of aromatic C–H bonds involving the new rhodium complex $[C_5(CH_3)_5]Rh[P(CH_3)_3](H)(C_6H_5)$.

Treatment of a 0.05 M THF solution of $[C_5(CH_3)_5]RhCl_2[P(CH_3)_3]$ with 1 equiv of 0.54 M $(p\text{-}C_6H_4X)MgBr$ in THF at −40 °C results in the formation of $[C_5(CH_3)_5]RhBr[P(CH_3)_3](C_6H_4X)$ in high yield (**1**, X = H; **2**, X = CH_3).[7] Preparative chroma-

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(5) If for the intramolecular oxidative addition $\Delta S^{\ddagger}_{intra} \simeq -5$ eu (small and negative) and for the intermolecular oxidative addition $\Delta S^{\ddagger}_{inter} \simeq -30$ eu and $\Delta H^{\ddagger}_{inter} \simeq \Delta H^{\ddagger}_{intra}$, then $\Delta\Delta G^{\ddagger} = \Delta G^{\ddagger}_{intra} - \Delta G^{\ddagger}_{inter} = T(\Delta S^{\ddagger}_{inter} - \Delta S^{\ddagger}_{intra}) = -7.5$ kcal/mol. See also: Ibers, J. A.; DiCosmo, R.; Whitesides, G. M. *Organometallics* **1982**, *1*, 13–20.

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