Asymmetric Additions to Chiral Naphthyloxazolines. An Entry into Tetracyclic Terpene Ring Systems Related to Aphidicolin, Scopadulcic Acid, and Kauranes

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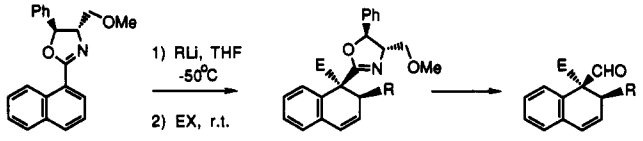
Received January 23, 1991

Summary: An asymmetric synthesis of the titled ring systems is described.

The utility of 2-naphthyl-(4*S*,5*S*)-4-(methoxymethyl)-5-phenyloxazolines **1** as chiral templates that undergo a tandem addition–alkylation with high diastereomeric excess furnishing naphthalene derivatives **2** has been previously reported.[2] The wide array of nucleophilic and electrophilic reagents amenable to this methodology leads to chiral nonracemic polysubstituted dihydronaphthalenes **3** in high (>95%) enantiomeric excess after detachment of the chiral auxiliary.[3] Our studies have continued wherein we are addressing the acquisition of more complex ring systems in enantiomerically pure form. A variety of tetracyclic rings are seen to be present in aphidicolin, the scopadulcic acids, or kauranes (vide infra), and this provided the impetus for us to ask whether these architecturally interesting molecular arrays could be accessed by this methodology.

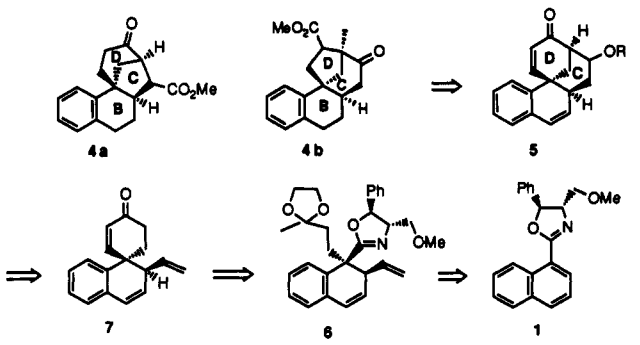


1 2 3

We now describe the potential utility of the tandem alkylation of chiral naphthyloxazolines to gain simultaneous entry into these *skeletal* ring systems in an enantioselective manner. The retrosynthetic approach to the tetracyclic nuclei **4a**, **4b** is shown in Scheme I. We envisaged that the pivotal tetracyclic β-hydroxy ketone **5**, containing two six-membered rings (C and D), could be assembled in high optical purity from addition of a vinyl nucleophile (vide infra) to the naphthyloxazoline **1** followed by capture with a suitably protected methyl vinyl ketone equivalent, thus affording the tandem alkylated derivative **6**. Unmasking the formyl group from the oxazoline followed by aldol condensation with the latent methyl ketone should furnish the spiro enone **7**. Elaboration of the vinyl appendage followed by regioselective cyclization to form the C ring would produce the common intermediate **5** needed to gain entry into the two isomeric skeletal systems **4a**, **4b**. It was our plan to exploit the differing oxidation states of the C and D rings in **5** and thus effect selective ring contraction. The tetracyclic nucleus **4a** would therefore arise from contracting the C ring, whereas system **4b** would be obtained by D-ring contraction.

On the basis of these perceptions, our initial goal was the asymmetric preparation of β-hydroxy enone **5** (R = H) in high enantiomeric purity (Scheme II). Toward that end, treatment of naphthyloxazoline[4] **1** with vinyltri-*n*-

Scheme I



4a **4b** **5** **7** **6** **1**

butylstannane[5] and methyllithium at −45 °C followed by capture of the resultant aza allyl anion with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane[6] afforded the bisalkylated adduct (+)-**6** (99%) as a single diastereomer after radial chromatography, $[\alpha]_D$ 227° (*c* 2.0, MeOH). Removal of the oxazoline auxiliary was effected by treatment of **6** with methyl triflate in CH_2Cl_2 followed by $NaBH_4$ reduction and subsequent hydrolysis (oxalic acid) to produce (+)-**8a** after radial chromatography, $[\alpha]_D$ 211.4° (*c* 0.88, MeOH).[7] The ketal was hydrolyzed by treatment with catalytic p-TsOH furnishing **8b**. Formation of (+)-**7** (in 78% overall yield from **1**) was accomplished by aldol condensation of the resultant dicarbonyl adduct and gave the spiro enone as a white crystalline solid, mp 115–117 °C, $[\alpha]_D$ 348° (*c* 1.20, MeOH). Hydroboration–oxidation[8] of the latter with excess 9-BBN and H_2O_2 furnished the allylic diol in quantitative yield as a mixture of diastereomers. Swern oxidation[9] of this diol followed by aldol condensation of the resultant keto aldehyde gave the tetracyclic ketols (−)-**9** in ~78% yield as a mixture of epimeric alcohols (1:1). This sequence was amenable to large-scale preparation and resulted in multigram quantities of the tetracyclic β-hydroxy enones (−)-**9** in 62% overall yield from the chiral 1-naphthyloxazoline **1**. The presence of epimeric alcohols **9** was of no consequence in the route leading to **4a** since the alcohols were to be transformed into the ketone (−)-**10**. However, (−)-**9** was separated into pure epimeric alcohols and assessed for their enantiomeric purity (isomer A mp 179–180 °C, $[\alpha]_D$ −103° (*c* 1.0, MeOH); isomer B mp 208–209 °C, $[\alpha]_D$ −45.9° (*c* 1.3, MeOH)). Analysis by chiral stationary-phase HPLC[10] and comparison to the racemate

(1) American Cancer Society Postdoctoral Research Fellow.
(2) Meyers, A. I.; Barner, B. A. *J. Am. Chem. Soc.* **1984**, *106*, 1865. Meyers, A. I.; Hoyer, D. *Tetrahedron Lett.* **1984**, *25*, 3607.
(3) For leading references and an example experimental procedure, see: Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.
(4) For leading references, see: Meyers, A. I.; Lutomski, K. A.; Laucher, D. *Tetrahedron* **1988**, *44*, 3107.
(5) It was found that use of vinyltri-*n*-butylstannane gave better results than using the tetravinylstannane as was previously employed. In addition, the synthesis of this starting material is considerably less complicated.
(6) Stowell, J. C. *J. Org. Chem.* **1983**, *48*, 5381.
(7) Complete characterizations of each compound in this sequence has been obtained. It is presently assumed that the absolute stereochemistry at the two stereocenters is correct as shown. This is based on over 20 cases of asymmetric tandem additions to **1** wherein no deviations from the observed facial selectivity were observed.[3]
(8) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2066.
(9) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(10) The stationary phase utilized was a Chiralcel OJ (cellulose based, Diacel Chemical Industries, Ltd.) column with 20% ethanol–hexanes as mobile phase. The excellent separation (>13 min) of the enantiomers is noteworthy. Okamoto, Y.; Hatada, K. *J. Chromatogr.* **1987**, *95*, 389.

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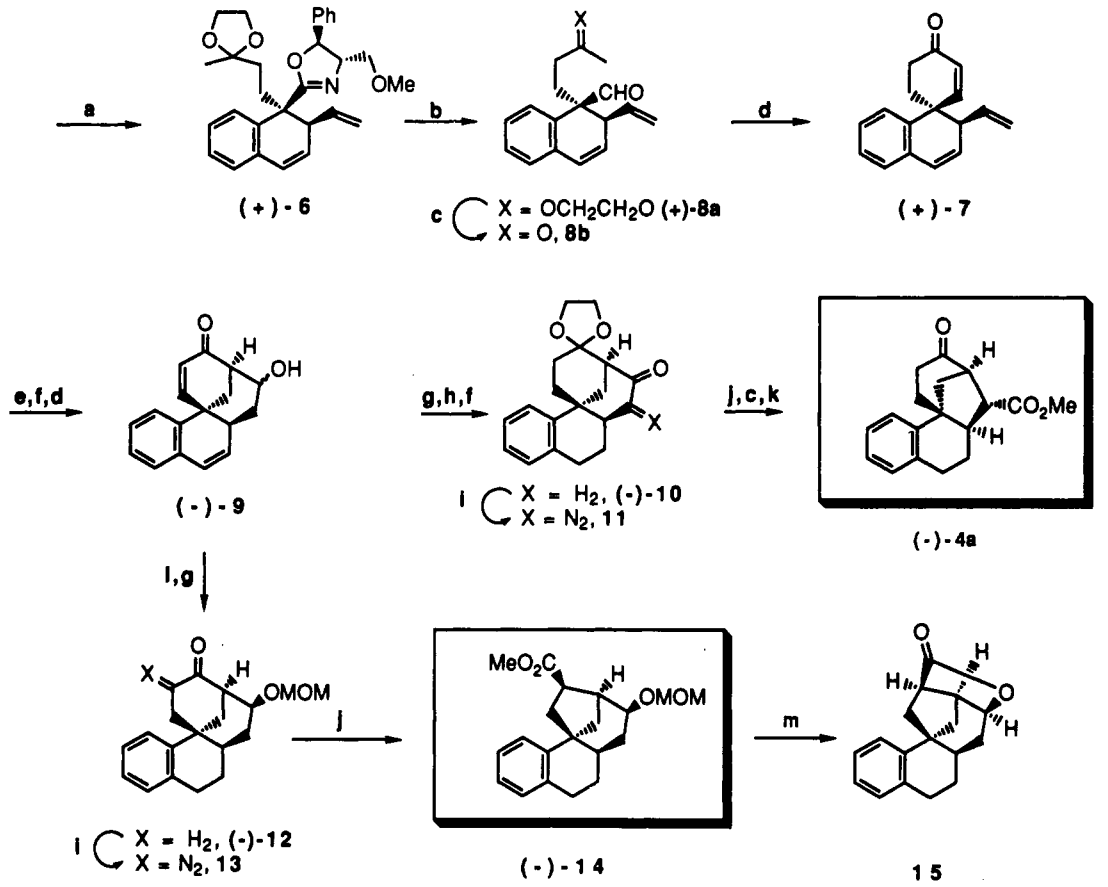
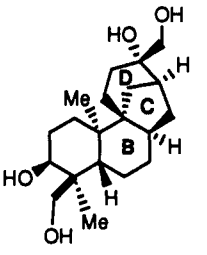
Scheme II[a]

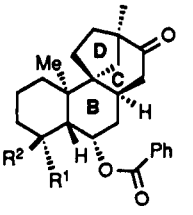


[a] Reagents and conditions: a, (i) MeLi, $Bu_3SnCH{=}CH_2$, −45 °C, THF, (ii) 2-methyl-2-(2-iodoethyl)-1,3-dioxolane, rt; b, (i) MeOTf, CH_2Cl_2, (ii) $NaBH_4$, MeOH–THF, (iii) H_3O^+; c, pTsOH; d, 2.5% KOH–MeOH, rt; e, 9-BBN, H_2O_2, 3 M NaOH, THF; f, Swern oxidation; g, Pd/C, H_2, MeOH; h, $HO(CH_2)_2OH$, pTsOH; i, $ArSO_2N_3$, KOH, PTC; j, $h\nu$, MeOH–Et_2O; k, NaOME–MeOH; l, MOMCl, NaH, THF; m, H_3O^+.

indicates that pure enone (−)-**9** was prepared in >97% ee.[11] Elaboration of (−)-**9** to the [3.2.1]bicyclic system **4a** was performed by hydrogenation (Pd/C) in MeOH followed by ketalization of the carbonyl group to produce the hydroxy ketal in 97% yield. Swern oxidation and subsequent α-diazo transfer[12] of the resultant ketone (−)-**10**, $[\alpha]_D$ −82.3° (*c* 1.14, MeOH) yielded the α-diazo ketone **11**. Irradiation of this material (Hg arc lamp, quartz, Et_2O/MeOH solvent, 1 h) resulted in Wolff ring contraction[13] in good yield (53% from (−)-**10**). Deketalization and equilibration[14] of the resultant keto esters with methanolic sodium methoxide gave (−)-**4a** as a single diastereomer in 90% overall yield, $[\alpha]_D$ − 27.5° (*c* 1.3, MeOH). The relationship of **4a** to the tetracyclic system present in aphidicolin[15] (specifically the BCD ring portion) with respect to relative stereochemistry is immediately evident.



APHIDICOLIN



SCOPADULCIC ACID
$R^1 = CO_2H$, $R^2 = CH_2OH$ Acid A
$R^1 = Me$, $R^2 = CO_2H$ Acid B

A somewhat similar approach was utilized to gain entry to the related tetracyclic system **4b**. Treatment of a single epimer of β-hydroxyenone (−)-**9** with MOMCl[16] followed by hydrogenation of both olefinic bonds yielded the ketone (−)-**12** in 73% overall yield, $[\alpha]_D$ −75.2 (*c* 0.80, MeOH). As described previously, α-diazo transfer and subsequent photolytic Wolff ring contraction of (−)-**13** gave a single methyl ester (−)-**14** in 59% yield, $[\alpha]_D$ −130.6° (*c* 0.98, MeOH), which was assigned with the β ester configuration on the basis of the fact that acidic removal of the MOM group resulted in formation of the cyclic lactone **15**. This lactonization should only be possible with the hydroxyl

(11) This enantiomeric purity was further supported by preparation of the *R* Mosher esters and subsequent examination of the racemate and optically pure derivatives by ^{19}F NMR. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(12) Lombardo, L.; Mander, L. N. *Synthesis* **1980**, 368.

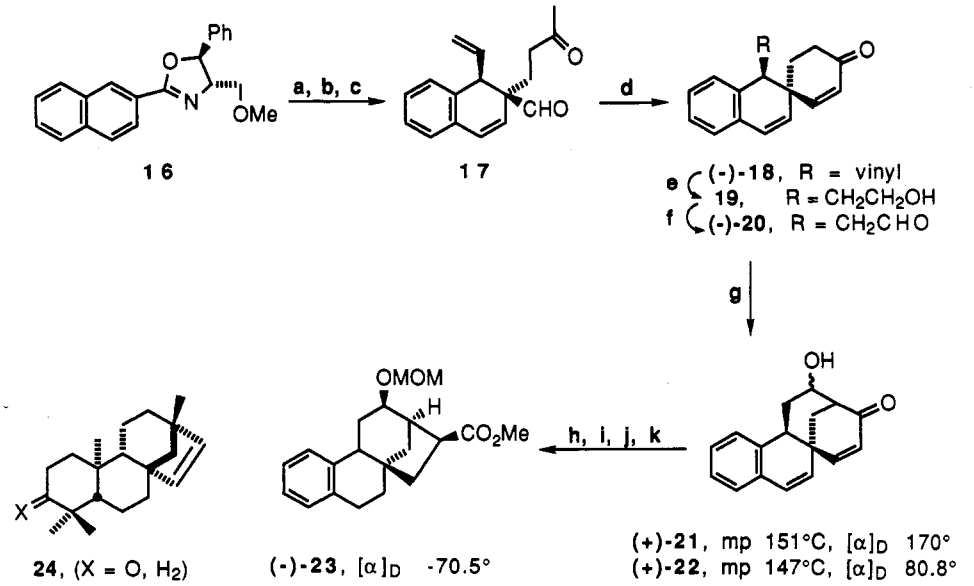
(13) Jones, M.; Ando, W. *J. Am. Chem. Soc.* **1968**, *90*, 2200.

(14) Models suggest strongly the α ester configuration to be most stable. Basic equilibration with catalytic NaOMe–MeOH takes place in a very short time to give a single diastereomer.

(15) (a) Isolation: Hesp, B. *J. Chem. Soc., Chem. Commun.* **1972**, 1027. Hesp, B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2841. (b) Biological activity: Starrett, A. M. *Can. J. Microbiol.* **1974**, *20*, 3416. Kawada, K. *Agric. Biol. Chem.* **1978**, *42*, 1611. Ohashi, M. *Biochem. Biophys. Res. Commun.* **1978**, *82*, 1084. (c) Total syntheses: Trost, B. M. *J. Am. Chem. Soc.* **1979**, 1328. McMurry, J. E. *J. Am. Chem. Soc.* **1979**, 1331. Corey, E. J. *J. Am. Chem. Soc.* **1980**, 1742. Ireland, R. E. *J. Am. Chem. Soc.* **1981**, 2446. Van Tamelen, E. E. *J. Am. Chem. Soc.* **1983**, 142. Bettollo, R. M. *Helv. Chim. Acta.* **1983**, 1922. Holton, R. A. *J. Am. Chem. Soc.* **1987**, 1597.

(16) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.

Scheme III[a]



[a] Reagents and conditions: a, MeLi, $Bu_3SnCH{=}CH_2$, THF, −50 °C; b, $ICH_2CH_2(Me)C(OCH_2)_2$; c, (i) MeOTf, $CHCl_2$, (ii) $NaBH_4$, MeOH–THF, (iii) H_3O^+; d, 2.5% KOH–MeOH; e, 9-BBN, H_2O_2, 3 M NaOH, THF; f, Swern oxidation; g, 2.5% KOH–MeOH, rt; h, MOMCl, NaH, THF; i, Pd/C, H_2, MeOH; j, $ArSO_3N_3$, KOH, PTC; k, *hν*, MeOH–Et_2O.

group and ester function on the β-face of **14**. This completed the assembly of the skeletal array related to the scopadulcic acids[17] from the common intermediate (−)-**9** in 44% overall yield. The relationship of **14** to our target **4b** is merely oxidation of the C-ring hydroxyl group.

Finally, we examined the additional scope of this method by utilizing the chiral oxazoline **16** derived from 2-naphthoic acid as an entry into the isomeric tetracyclic system **24**. The latter is present in a number of kaurane diterpene systems such as hibaene[18] and stachenone.[19] Scheme III outlines our route, which is purposely similar to the route previously described (in Scheme II). The acquisition of optically pure tetracyclic ketones **21**, **22** in good overall yield was the principal goal of this aspect of the study and as Scheme III depicts, we have reached this goal. The epimeric ketones could be readily separated (formed in the aldol process as a 1:1 mixture) and characterized. These were carried forward to the model tetracyclic carboxylic esters **23**. Although the last two steps; the α-diazo transfer and subsequent photolysis to the product **23** have not been optimized (27% over both steps), we are comfortable with the overall sequence and versatility shown by the chiral naphthyloxazolines **1** and **16**.

Methodology such as this, although not necessarily in position to reach specific natural products, is considered to be worthy of merit in synthesis. A similar report by Overman[20] nicely demonstrated how general ring closure strategy via palladium-catalyzed polyene cyclizations can provide an entry into the tetracyclic system **4b**, namely the scopadulcic acid skeletal system. The enantioselectivity, efficiency, and simplicity of this approach attest to the potential power of this process. We are continuing our efforts to reach complex systems and are in the process of making appropriate modifications in starting materials.[21]

Acknowledgment. We are grateful to the National Institutes of Health for support of this program.

Supplementary Material Available: Experimental details and physical constants for all compounds (15 pages). Ordering information is given on any current masthead page.

(17) Hayashi, T.; Kishi, M.; Kawasaki, M.; Arisawa, M.; Shimizu, M.; Suzuki, S.; Yoshizaki, M.; Morita, N.; Tezuka, Y.; Kikuchi, T.; Berganza, L. H.; Ferro, E.; Basualdo, I. *Tetrahedron Lett.* **1987**, *32*, 3693.
(18) Ireland, R. E.; Mander, L. N. *Tetrahedron Lett.* **1965**, 2627.
(19) Monti, S. A.; Yang, Y.-L. *J. Org. Chem.* **1979**, *44*, 897 and earlier references cited.
(20) Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328.
(21) The installation of the angular methyl at C-10 (aphidicolin numbering) is a major goal of the presently ongoing studies. We would like to *stress* that utilization of the reported approach (from the naphthalene nucleus) to a natural product system containing this C-10 angular methyl group is obviously neither facile nor attractive. Efforts utilizing more appropriately functionalized A and B rings (e.g., 10-methyldecalones) in place of naphthyl systems are currently under study, and preliminary results are encouraging.

Multiple Rearrangements of 1-Methoxyfluorenylidene to 1-Phenanthrenol

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Received November 27, 1990

Summary: Flash vacuum pyrolysis of 1-methoxy-9-diazofluorene (**1**) yielded 1-phenanthrenol (**2**). Experiments with ^2H- and ^{13}C-labeled **1** revealed that the source of C_{10} of **2** is the methoxy carbon of **1**, whereas the likely source of C_9 of **2** is the diazo-substituted carbon of **1**.

The rearrangements of arylcarbenes[1] in the gas phase are of a complexity that rivals that of the rearrangements of carbocations in solution. Even innocent-looking products may have been produced by a long series of rearrangements and automerization. Such rearrangements

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