intractable material upon continued heating, whereas the minor isomer rapidly cyclized.) Alternatively, the isomeric mixture of ketones **8** can be used directly to provide isoxazolidine **5** in 75% yield.

Completion of the hirsutene total synthesis requires stereospecific reductive deamination. We chose a Cope elimination–hydrogenation sequence to effect this transformation. Thus, methylation (xs MeI) of isoxazolidine **5** and subsequent N–O scission (H_2/Pd) gave amino alcohol **9** (89% overall yield). Cope elimination of the corresponding amine oxide (MCPBA, CH_2Cl_2, aqueous $NaHCO_3$, 50 °C, 48 h; 90%) gave only **10** and none of the regioisomeric elimination product with the double bond endocyclic to both rings (>98:2 by ^{13}C NMR spectral analysis). Although the factor(s) responsible for this selectivity are not evident, it should be noted that the olefin moiety in **10** offers access to the C-11 α-hydroxyl present in coriolin. The synthesis was concluded by oxidation of alcohol **10** followed by stereospecific hydrogenation to furnish the known ketone **11** (65%) which was identical in all respects (IR, ^1H 360-MHz NMR, ^{13}C NMR, mp) with an authentic sample and spectra kindly furnished by Professors Hudlicky and Curran. Ketone **11** has been previously converted to *dl*-hirsutene (**1**) by reaction with methylenetriphenylphosphorane.[3a]

In summation, we have reported a new strategy for the stereospecific and expedient assemblage of the linearly fused tricyclopentanoid framework. The versatility of this methodology remains to be documented and consequently we are investigating its further application.

Acknowledgment. We thank the National Science Foundation (CHE-8205144) for financial and material support. High-field (360 MHz) ^1H and ^{13}C NMR spectra were obtained on a spectrometer purchased with funds provided, in part, by the National Science Foundation (CHE80-24328); mass spectra were obtained through the National Science Foundation Regional Mass Spectroscopy Center at the University of Nebraska (CHE-82-11164).

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Directed Ortho Metalation Induced Epoxy Cyclialkylation. Regiospecific 5-Exo-Tet and 6-Exo-Tet Routes to Benzofurans and Benzopyrans

Summary: Metalation of epoxybenzamides **7a–d**, **11**, **13**, **15** occurs by regiospecific 5-exo-tet and 6-exo-tet ring-closure modes and leads to benzofuran and benzopyran derivatives **8a–d**, **12**, **14**, **16**.

Sir: Strategies for carbon–carbon bond-forming annelation to an aromatic ring are generally based on Friedel–Crafts methodology[1] and are therefore dictated by the rules of classical aromatic electrophilic substitution. The anionic equivalent of the Friedel–Crafts and related reactions (Scheme I, **1a,b** → **2a,b** → **3a,b**) discovered by Parham[2] constitutes a new concept with broad, as yet unexploited, synthetic potential[3] which, however, is dependent on the metal–halogen exchange process and thus on the availability of ortho-bromo substituted reactants. Likewise dependent and synthetically underdeveloped is the anionic epoxy cyclialkylation variant[4,5] **1c** → **2c** → **3c** recently disclosed by Bradsher[6] and by Durst.[7] Herein we report on a new anionic heteroring epoxy cyclialkylation **4** → **5** → **6** whose regiospecificity originates solely with the powerful directed ortho metalation character of the tertiary amide function.[8] This method, following 5-exo-tet and 6-exo-tet modes,[9] provides a useful and potentially general protocol for the construction of unusually substituted benzofuran and benzopyran systems.

Scheme I

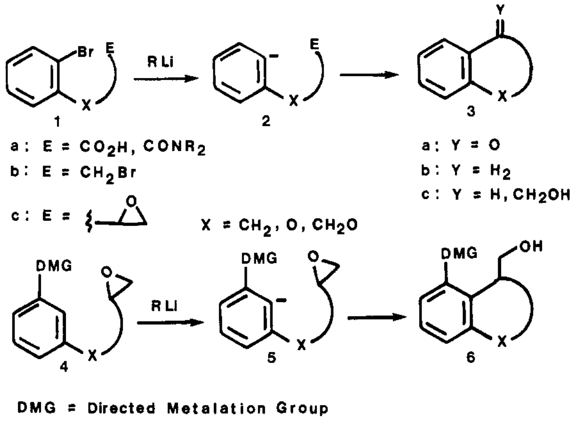

Table I. Directed Ortho Metalation Induced Epoxy Cyclialkylations

substrate	product	yield,[a] %	mp, °C
7a	**8a**	67	*b*
7b	**8b**	60	*b*
7c	**8c**	64	133–134[c]
7d	**8d**	68	90–91[c]
11	**12**	53	115–116[c]
13	**14**	65	103–105[c]
15	**16**	32	*b*
17	**18**	38	*b,d*

[a] Yields correspond to purified (silica gel chromatography (hexane–EtOAc) or crystallization) materials. [b] Oil, purified by chromatography, homogeneous by TLC in several solvent systems. [c] Recrystallized from CH_2Cl_2–hexane. [d] 3 equiv of *sec*-BuLi/TMEDA were required to effect cylization.

Standard metalation (1.5 equiv of *sec*-BuLi/TMEDA/THF/−78 °C)[8] of **7a**[10,11] followed by warming to am-

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[1] Olah, G. A. Ed. "Friedel–Crafts and Related Reactions"; Interscience; New York, 1963; Vol. I–IV.

[2] Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300.

[3] This potential is in the early stages of exploitation: Boatman, R. J.; Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1977**, *99*, 4822. Kometani, T.; Takeuchi, Y.; Yoshii, E. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1197.

[4] The corresponding epoxy cyclialkylation of α-stabilized carbanions is a well-established synthetic tactic: Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323. Decesare, J. M.; Corbel, B.; Durst, T.; Blout, J. F. *Can. J. Chem.* **1981**, *59*, 1415 and references cited therein.

[5] The Lewis acid promoted epoxy cyclialkylation is receiving initial attention: (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.* **1983**, *48*, 4572. (b) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. *J. Org. Chem.* **1983**, *48*, 2449.

[6] Bradsher, C. K.; Reames, D. C. *J. Org. Chem.* **1978**, *43*, 3800.

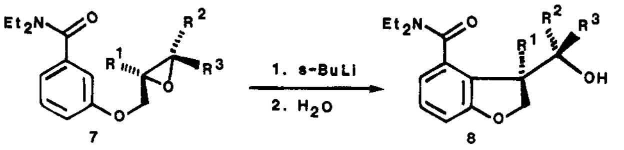
[7] Dhawan, K. L.; Gowland, B. D.; Durst, T. *J. Org. Chem.* **1980**, *45*, 922.

[8] Review: Beak, P.; Snieckus, V. *Acc. Chem. Res.* **1982**, *15*, 306.

[9] Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

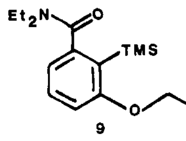
[10] Epoxy amides **7a–e**, **11**, **13**, **15** and **17** were prepared in 70–80% yields from *N,N*-diethyl-3-methoxybenzamide as follows: (1) $BBr_3/CH_2Cl_2/-78$ °C → RT/14 h; (2) $NaH/R^3R^2C{=}C(R^1)CH_2Br/DMF/0$ °C → RT/6 h; (3) $MCPBA/CH_2Cl_2$/RT/24–48 h and purified by column chromatography (silica gel, hexane–Et_2O) before use.

bient temperature over 10 h gave the carbinol amide **8a** in good yield (Table I). Its structure was established by



7 8

a: $R^1 = R^2 = R^3 = H$; b: $R^1 = R^3 = H$, $R^2 = Me$; c: $R^1 = R^3 = H$, $R^2 = Ph$; d: $R^1 = H$, $R^2 = R^3 = Me$; e: $R^1 = Me$, $R^2 = R^3 = H$



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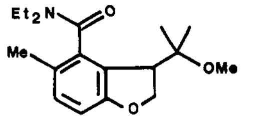

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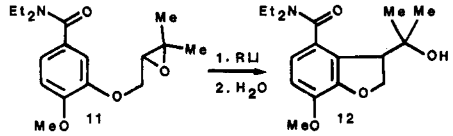
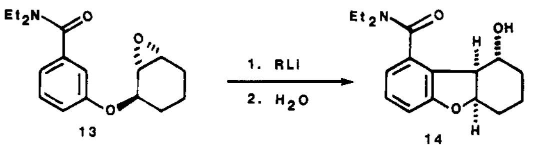
detailed ^1H and ^{13}C NMR spectroscopic examination and comparison with data for known systems.[6,11,12] Using identical conditions, the epoxy amides **7b,c,d** were cyclized to afford **8b,c,d**, respectively.[11] These reactions are in harmony with Baldwin's guidelines of 5-exo-tet ring closure,[9] i.e., the geometry demanded by the colinear carbanion–epoxide transition state favors five-membered ring formation. The observed regiospecific in-between metalation may be enhanced by additional lithium–epoxide oxygen coordination effects. Application of the same reaction conditions to **7e** led to decomposition and recovery of starting material (13%). That the formation of the metalated species required for cyclization had occurred was demonstrated by quenching a THF solution of the mixture of **7e** and *sec*-BuLi/TMEDA at −78 °C with TMSCl to produce the trimethylsilyl derivative **9** (53%).[11] Thus the preferred 5-exo-tet cyclization is sterically impeded by the methyl substituent.[13] The synthetic potential of the epoxy cyclialkylation for substituted and annelated benzofurans[14] is illustrated by the smooth conversions of **11**[10] and **13**[10] into products **12**[11] and **14**,[11] respectively.



11 12

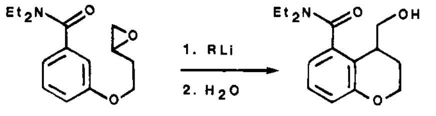


13 14

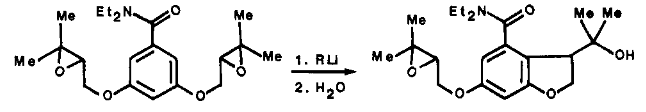
The homologous epoxy amide **15**[10] was subjected to the same cyclization conditions to give the benzopyran derivative **16**[11] following the preferred 6-exo-tet mode.[9]

In order to explore further directed metalation possibilities in these poorly accessible 4-carbon substituted benzofurans **8**,[14] the most favorable case **7d** was sequentially lithiated (1.1 equiv of *sec*-BuLi/TMEDA) warmed to room temperature, cooled, lithiated under the standard conditions, and methylated (excess MeI) in one pot. The product 5-methylbenzofuran **10**,[11] although obtained in modest yield (45%) and suffering from *O*-methylation, is a preliminary indication of additional potential of the ortho metalation initiated epoxy cyclialkylation in synthesis.

Bis epoxy cyclialkylation of **17**[10] was explored under the above conditions except that 3 equiv of *sec*-BuLi was used.



15 16



17 18

The monocyclized product **18**[11] was obtained (38% yield). Attempts to effect the second cyclization (3 equiv of *sec*-BuLi/TMEDA/−78 °C → room temperature overnight) failed. This failure undoubtedly resides in the inherent strain which would be imposed by the second dihydrofuran ring closure.[2]

This new anionic epoxy cyclialkylation methodology coupled with additional metalation potential (**7d** → **10**) augers well for the expansion of the directed ortho metalation strategy[8] toward regiospecific synthesis of systems not readily achievable by electrophilic substitution chemistry.[5b,15,16]

Registry No. **7a**, 93280-60-5; **7b**, 93280-61-6; **7c**, 93280-62-7; **7d**, 93280-63-8; **7e**, 93280-64-9; **8a**, 93280-65-0; **8b**, 93280-66-1; **8c**, 93280-67-2; **8d**, 93280-68-3; **9**, 93280-69-4; **11**, 93280-70-7; **12**, 93280-74-1; **13**, 93280-71-8; **14**, 93280-75-2; **15**, 93280-72-9; **16**, 93280-76-3; **17**, 93280-73-0; **18**, 93280-77-4.

Supplementary Material Available: ^1H NMR spectra for compounds **8b–d**, **9**, **10**, **12**, **14**, **16**, and **18** (2 pages). Ordering information is given on any current masthead page.

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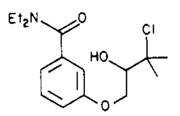
[11] All new compounds show satisfactory combustion analyses and spectral (IR, ^1H and ^{13}C NMR, MS) data fully consistent with the assigned structures.

[12] Salient features of the NMR spectra of **8a**: ^1H NMR (400 MHz, $CDCl_3$) δ 3.46 (m, 1 H), 3.73 (m, 2 H), 4.44 (dd, 1 H, J = 5.6, 9 Hz), 4.63 (t, 1 H, J = 9.0, 9.0 Hz), 6.80 (q, 1 H, J = 0.7, 7.4 Hz), 6.83 (d, 1 H, 8.0 Hz), 7.17 (t, 1 H, J = 7.8, 8.0 Hz). The site of cyclization was unambiguously assigned by comparison of the aromatic regions of the ^{13}C NMR spectra of epoxides **7** and benzofuran products **8** by using the established additivity of substituent effects and comprehensive data available for a series of benzamides (Beak, P.; Brown, R. A. *J. Org. Chem.* **1982**, *47*, 34), e.g., ^{13}C NMR δ exptl (calcd, assignment) **7a**: 138.7 (138.3, C-1), 112.6 (111.7, C-2), 158.5 (159.5, C-3), 115.7 (114.5, C-4), 129.6 (129.4, C-5), 119.0 (118.6, C-6). **8a** (C-numbering corresponding to **7a**): 134.0 (C-1), 124.9 (C-2), 161.4 (C-3), 110.4 (C-4), 128.8 (C-5), 117.7 (C-6).

[13] An attempt to effect 6-endo ring closure on compound **7d** by prior epoxide coordination with $MgBr_2$ (2.5 equiv) according to the procedure of Durst[7] followed by metalation with *sec*-BuLi with and without TMEDA led only to the formation of **8d** in lower yield (31%).

[14] Mustafa, A. "Benzofurans, The Chemistry of Heterocyclic Compounds"; Weissberger, A., Taylor, E. D., Eds.; Wiley: New York, 1974.

[15] This point is further emphasized by the fact that under the widely used Friedel–Crafts reaction conditions ($TiCl_4/CH_2Cl_2$/−78 °C → RT/4 h), **7d** gave the chlorohydrin i.[11]



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[16] We are grateful to NSERC Canada for continuing financial support of research.