ORGANIC LETTERS

2003
Vol. 5, No. 6
831−834

Dearomatizing Cyclization of Arylsulfonylalkoxymethyl Lithiums: A Route to the Podophyllotoxin Skeleton

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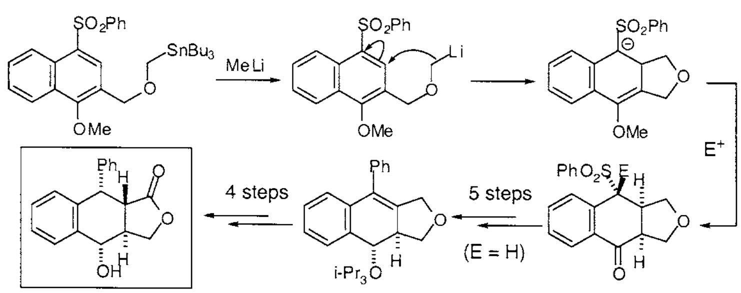
Received January 13, 2003

ABSTRACT



The phenylsulfonyl group promotes the dearomatizing cyclization of tethered organolithiums onto aromatic rings. With an ether tether, the cyclizations create a new tetrahydrofuran ring, and both cyclization and subsequent electrophilic quenches proceed with high levels of diastereoselectivity. The sulfonyl group can be removed from the cyclized products oxidatively or reductively. The dearomatizing cyclization of a naphthyl sulfone was used in the synthesis of a close structural analogue of podophyllotoxin.

Dearomatizing additions to aromatic systems[1] allow the stereocontrolled formation of cyclohexene and cyclohexanone derivatives with regiocontrol offered by aromatic substitution chemistry and with stereochemistry controlled in the addition step. While Birch reduction generates nucleophilic partially saturated arene derivatives that react with electrophiles,[2] polarity-reversed synthetic equivalents to the Birch reduction in which nucleophiles are added to electrophilic[3] aromatic (particularly naphthyl) rings are also known. When the nucleophile is intramolecular, a dearomatizing cyclization reaction ensues,[4,5] allowing the stereoselective synthesis of ring-fused molecules. We used dearo-

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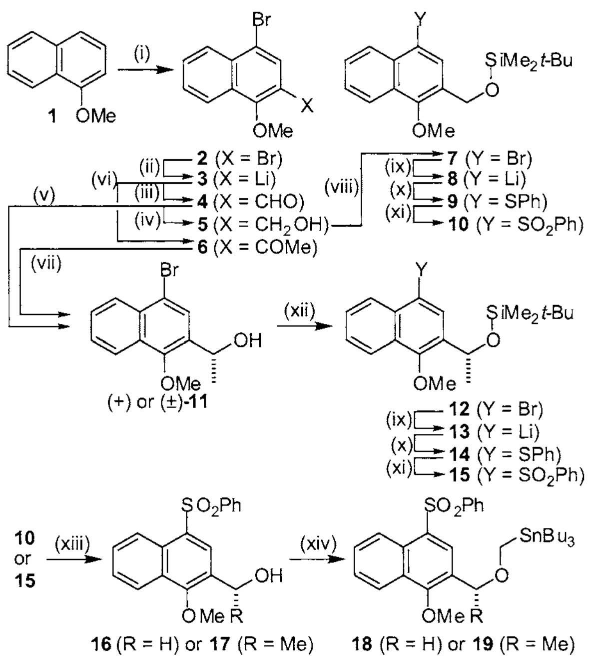
10.1021/ol0340585 CCC: $25.00
Published on Web 02/26/2003

matizing cyclization of lithiated amides to make intermediates for the synthesis of kainoid amino acids,[6] and recently we reported cyclization of some lithiated oxazolines.[7]

A scattered handful of reports[8] suggested to us that the dearomatizing cyclization of lithiated sulfones and sulfonamides might also be generalized into a valuable synthetic method and that we might be able to capitalize on the versatility of sulfone chemistry[9] in the transformation of the products into useful targets. In this paper, we report that organolithiums tethered to aryl sulfones cyclize with dearomatization and describe the transformation of the products of this reaction into an analogue of the anticancer agent podophyllotoxin.

The starting materials **18** and **19** (Scheme 1) for the cyclization were made straightforwardly from 1-methoxy-

Scheme 1. Synthesis of the Cyclization Precursor[a]



[a] Reagents: (i) Br_2, CH_2Cl_2 100%; (ii) *n*-BuLi (0.95 equiv), Et_2O, −78 °C; (iii) Me_2NCHO; (iv) $NaBH_4$, MeOH, 84% from **2**; (v) MeLi, THF, −78 °C, 88% (±)-**11**; (vi) MeCON(OMe)Me, 57%; (vii) CBS reagent, BH_3:SMe_2, THF, 99% (+)-**11** (95% ee); (viii) *t*-BuMe$_2$SiCl, DMAP, Et_3N, CH_2Cl_2, 90%; (ix) *n*-BuLi, THF, −78 °C; (x) Ph_2S_2, 92% **9** from **7**; (xi) *m*-CPBA, EtOAc, $NaHCO_3$, 93% **10**, or $Na_2B_2O_6$, AcOH, 80% **15** from **12**; (xii) *t*-BuMe$_2$SiOTf, lutidine, CH_2Cl_2, 0 °C, 93%; (xiii) Bu_4NF, THF, 94% **16** from **10**, 62% **16** from **7**, or 98% **17** from **15**; (xiv) NaH, THF, then Bu_3SnCH_2I, 75% **18** or 60% **19**.

naphthalene **1** by bromination and selective bromine−lithium exchange[10] of **2** to yield the more stable monolithio species **3**. Formylation with DMF, reduction to **5**, and protection gave the silyl ether **7**. A second bromine−lithium exchange, trapping with diphenyl disulfide, and oxidation gave the sulfone **10**, which was deprotected. Alkylation of **16** with iodomethyltributylstannane[11] gave the cyclization precursor **18**. A parallel route gave the chiral stannane **19**: enantiomerically enriched material was obtained by CBS reduction[12] (to **11**) of the ketone **6** derived by Weinreb acylation[13] of **3**; **11** was obtained in racemic form by addition of MeLi to aldehyde **4**. Protection, introduction of the sulfone, and deprotection gave alcohol **17** and hence the stannane **19**, in both racemic and enantiomerically enriched[14] forms.

Treatment of a THF solution of **18** with methyllithium in the presence of TMEDA promoted transmetalation to the organolithium **20** (Scheme 2). Even at −78 °C, this organolithium cyclized to **21** by attack on the naphthyl ring: quenching the orange anion **21** with a solution of NH_4Cl returned the unstable tricyclic enol ether *exo*-**22a** as a single diastereoisomer in 60% yield. Hydrolysis of the enol ether to ketone *exo*-**23a** (obtained in 69% yield) was accompanied by a small amount (10%) of epimerization to *endo*-**23**. This diastereoisomer was obtained as the only product when the reaction mixture, instead of being quenched with ammonium chloride quench at −78 °C, was warmed to 20 °C with methanol. A different unstable enol ether, presumably *endo*-**22**, was observed in the crude reaction mixture, and acid hydrolysis gave solely the ketone *endo*-**23** in 59% yield. X-ray crystal structures (Figure 1a,b) proved the stereochemistry of the products. Epimerization of the sulfonyl group to the endo face appears to be due to warming in the presence of methoxide, though it is not clear why *endo*-**22** should be more stable than *exo*-**22a**.

Alkylation of the sulfone anion **21** followed by hydrolysis gave good yields of single diastereoisomers of alkylated ketones **23b**−**d**, all with the same relative stereochemistry: the sulfonyl group in **23a**−**d** occupies the *exo* face of the cis-fused tricycle.[15]

Cyclization of the chiral stannane **19** was fully diastereoselective at both new stereogenic centers when the inter-

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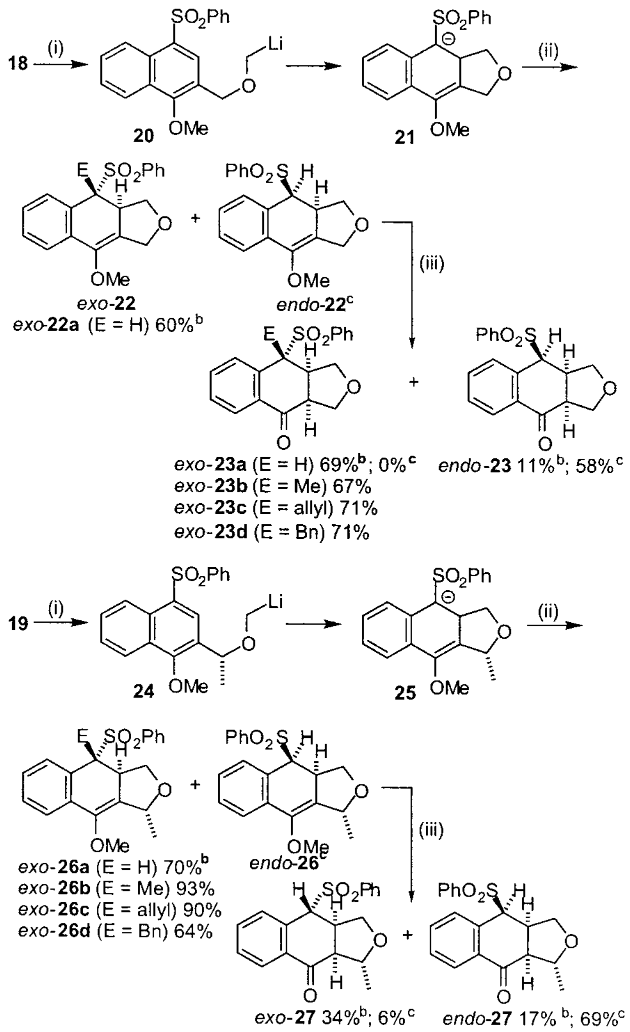
(14) Ee of 95% determined by HPLC (Whelk-O1).

(15) Stereochemistry of alkylated compounds *exo*-**23b**−**d** was deduced from the X-ray crystal structures of *exo*-**23b** and *exo*-**23d**.

Scheme 2. DearomatizIng Cyclizations[a]



[a] Reagents: (i) MeLi, TMEDA, THF, −78 °C; (ii) $E^+ = NH_4Cl$ (−78 °C) or MeOH (from −78 to 20 °C), MeI, allyl bromide or BnBr; (iii) 2 M HCl (aq). [b]From NH_4Cl quench. [c]From MeOH quench.

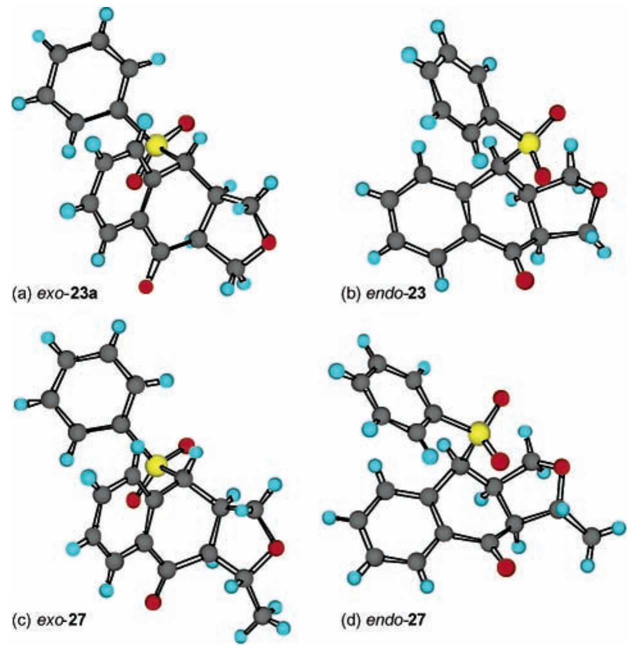
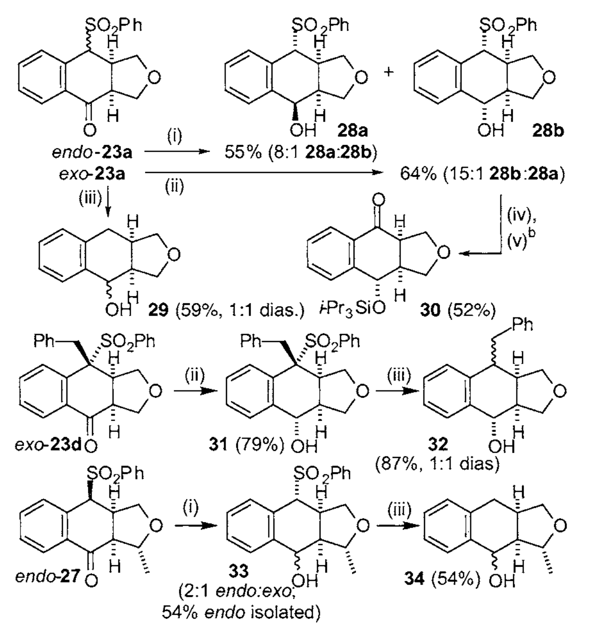


Figure 1. X-ray crystal structures of cyclized sulfones.

mediate **25** was alkylated. Good yields of single diastereoisomers of the stable enol ethers *exo*-**26b**−**d** were obtained, in which the methyl group α to oxygen occupies the *exo* face during the cyclization and the sulfone adopts the *exo* face during the alkylation. As with **18**, protonation with NH_4-Cl returned diastereoisomer *exo*-**26a**, which hydrolyzed to give ketone *exo*-**27** (97% ee), while protonation by warming with MeOH gave predominantly a different (presumably *endo*) diastereoisomer of the enol ether **26**, which hydrolyzed to give mainly the ketone *endo*-**27** (94% ee) bearing the sulfonyl group on the *endo* face.[16] Figure 1c,d shows the X-ray crystal structures of *exo- and endo*-**27.**

Sulfones are valuable synthetic intermediates because once the anion-stabilizing ability of the sulfonyl group has been exploited, it can be disposed of by oxidation, reduction, or elimination.[9] Scheme 3 shows some representative reductive and oxidative transformations of cyclized sulfones **23** and **27**. The sulfonyl group of both exo and endo sulfones appears

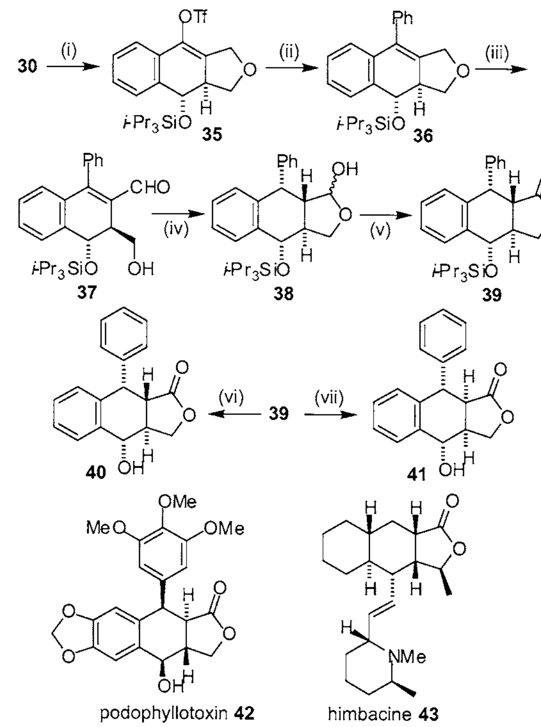
Scheme 3. Desulfonylations of the Products[a]



[a] Reagents: (i) $LiBHEt_3$, THF; (ii) $NaBH_4$, MeOH; (iii) Na/Hg, MeOH, Na_2HPO_4; (iv) *i*-Pr_3SiOTf, lutidine, CH_2Cl_2, 0 °C, 72%. (v) (1) *n*-BuLi, THF, −78 °C; (2) MoO_5•py•DMPU ("MoOPD"), THF, 72% (99% based on recovered starting material, which is enriched in **28a**). [b]**28b** made by $LiBHEt_3$ reduction of *exo*-**23a** and not isolated before protection. Only **28b** was silylated; **28a** was removed as an alcohol.

(16) Ee of *exo*-**27** was deduced from the ee of an enone byproduct formed in 34% yield by 5-*endo-trig* retro-Michael elimination of alkoxide from *exo*-**27**. An X-ray crystal structure of this byproduct confirmed the absolute stereochemistry of **19** and **24**−**27**. The ees of this byproduct and of *endo*-**27** were determined by HPLC (Whelk-O1).

Scheme 4. Synthesis of the Core Skeleton of Podophyllotoxin[a]



[a] Reagents: (i) (1) LiHMDS, THF, −78 °C; (2) 5-chloropyridylNTf$_2$, THF, from −78 to 20 °C, 91% (97% based on recovered starting material). (ii) PhB(OH)$_2$, Pd(PPh$_3$)$_4$, K$_3$PO$_4$, KBr, dioxane, 90 °C, 90%. (iii) (1) *t*-BuLi, THF, −78 °C; (2) Davis' oxaziridine (PhCH(O)NTs), THF, 56% (69% based on recovered starting material); (iv) H$_2$, Pd/C, EtOH, 57% + 27% diol from over-reduction; (v) PCC, CH$_2$Cl$_2$, 72%; (vi) HF:py, MeCN, 62%; (vii) Bu$_4$NF, THF, 72%.

to shield very effectively one face of the ketone (see Figure 1), allowing stereoselective reduction of *exo*- and *endo*-**23a** to **28a** and **28b**,[17] respectively, and of *exo*-**23d** to **31**. In the reduction of *endo*-**27** with lithium triethylborohydride, epimerization of the endo sulfone to exo competed with the reduction and gave a mixture of diastereoisomers **33**. Desulfonylation of **31** and **33** with sodium amalgam gave good yields of the tricyclic alcohols **32** and **34**; direct reduction of the ketosulfone *exo*-**23a** promoted both desulfonylation and nonstereoselective reduction of the ketone to give **29**. Oxidative removal of the sulfone[18] was also possible, and the lithio derivative of a protected form of sulfone **28b** reacted cleanly with the DMPU equivalent of MoOPH ("MoOPD")[19] to yield ketone **30**.

The 6,6,5-tricyclic system present in these desulfonylated products is also found in lignan and alkaloid natural products such as podophyllotoxin **42**[20] and himbacine **43**.[21] We were able to convert **30** into a known skeletal analogue **40**[22] of podophyllotoxin, with full relative stereochemical control.

Conversion of ketone **30** to the enol triflate **35**[23] allowed us to introduce the aryl substituent of **36** by a Suzuki coupling.[24] Oxidation of this allylic ether was attempted under a number of conditions, and the most successful method we found was to deprotonate **36** with t-BuLi, oxidizing the anion with Davis' oxaziridine[25] to yield the aldehyde **37**. Careful hydrogenation (over-reduction was always a problem) of **37** gave trans hemiacetal **38** with introduction of hydrogen trans to the bulky i-Pr$_3$SiO group and perhaps also directed syn by the primary alcohol. Oxidation to the lactone with pyridinium chlorochromate and deprotection with HF-pyridine yielded **40**,[26] a structural analogue of the core tetracycle of podophyllotoxin. Deprotection under more basic conditions (Bu$_4$NF, THF) caused a precedented[27] epimerization α to the lactone carbonyl and gave **41**, an analogue of picropodophyllin.[20]

Acknowledgment. We are grateful to the EPSRC and to Knoll-BASF Pharma for support.

Supporting Information Available: Experimental procedures and characterization for new compounds and X-ray data for *exo*-**23a**, *endo*-**23**, *exo*-**27**, *endo*-**27**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0340585

(17) Alcohol **28a** has the relative stereochemistry (proved by the X-ray crystal structure) of epipodophyllin, the lignan component of the drug's etoposide and teniposide (see ref 20)

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