ORGANIC LETTERS

2002
Vol. 4, No. 5
787−790

Dearomatizing Annelation of Five-Membered Rings to Naphthalenes by Organolithium Cyclization

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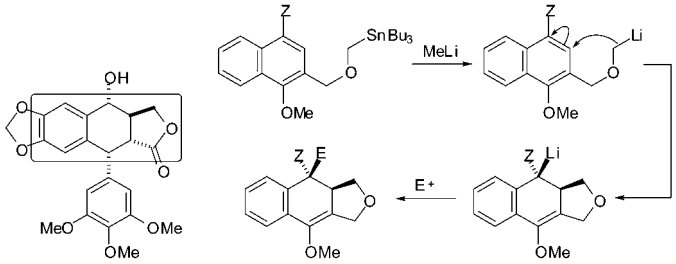
Received December 19, 2001

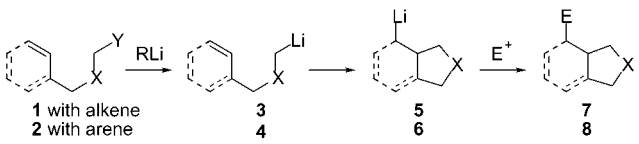
ABSTRACT



γ-Lithiopropylnaphthalenes and their oxa- and aza-tethered analogues cyclize by nucleophilic addition of the organolithium to the naphthalene ring. The resulting benzyllithiums react stereoselectively with electrophiles to give dearomatized tricyclic products with structural similarity to the arylnaphthalene lignans.

The cyclization of hexenyllithiums **3** and their oxa and aza analogues to give cyclopentanes,[1] tetrahydrofurans,[2] and pyrrolidines[3] **7** is now an established alternative to radical chemistry for the synthesis of five-membered rings (Scheme 1). Analogous cyclizations onto an aromatic ring (**2** → **4** → **6** → **8**) would provide valuable 6,5-fused ring systems, but despite a number of isolated reports in the literature,[4] no general method exists for this type of cyclization.[5] We have previously shown that similar cyclizations are possible when amide groups stabilize both starting and product organolithiums.[6] In this paper, we report that the anionic cyclization of unstabilized lithioalkylnaphthalenes and their oxa and aza analogues allows the dearomatizing annelation of a cyclopentane, tetrahydrofuran, or pyrrolidine ring to a naphthalene nucleus.

Scheme 1. Anionic Cyclization



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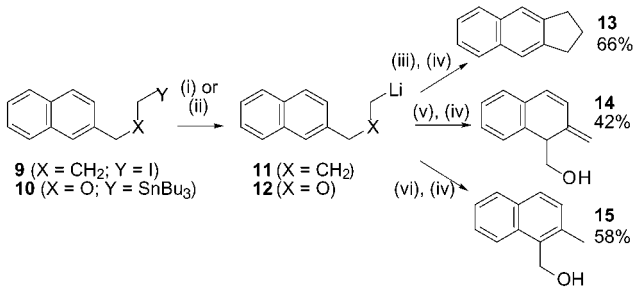
10.1021/ol0172626 CCC: $22.00
Published on Web 02/13/2002

Naphthalene itself reacts with organolithiums at the 2-position, but rearomatization of the organolithium adduct to give 2-alkylnaphthalenes is unavoidable.[7] To establish whether an intramolecular version of this reaction was feasible, we treated 2-(γ-iodopropyl)naphthalene **9** with *t*-BuLi in pentane/ether.[8] Addition of TMEDA promoted cyclization on warming to room temperature[9] (Scheme 2).

Scheme 2. Naphthalene Cyclization and Rearrangements[a]



[a] (i) (**9**) *t*-BuLi, pentane−Et_2O, −78 °C; (ii) (**10**) MeLi, THF, TMEDA, −78 °C; (iii) TMEDA, −78 → 20 °C; (iv) NH_4Cl; (v) 2 h, −78 °C; (vi) −78 → 20 °C.

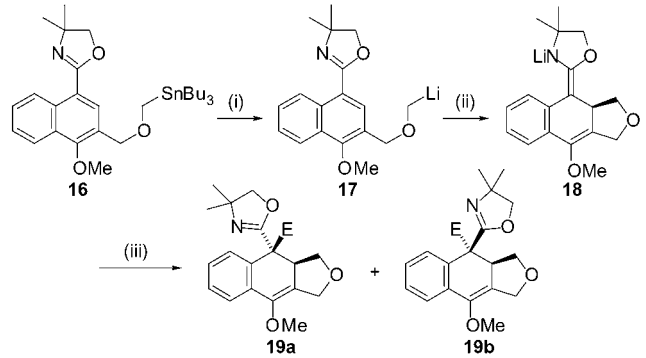
Cyclized but rearomatized compound **13** was obtained in good yield, and we were unable to trap a dearomatized organolithium by alkylation. Nonetheless, the reaction represents a rare example of anionic cyclization of an unfunctionalized organolithium onto an aromatic ring.[10]

Attempted cyclization of the oxa analogue **12**, formed by tin−lithium exchange from **10**, resulted in a dearomatizing [2,3]-Wittig rearrangement.[11] Unstable dearomatized compound **14** was isolated on quenching the reaction at −78 °C. Warming the solution to room temperature before quenching led to rearomatization to give **15** (Scheme 2).

To increase the electrophilicity of the naphthalene ring, we decided to incorporate an electron-withdrawing group into the 1-position. Electron-deficient naphthalenes readily undergo nucleophilic addition to give dearomatized products.[12] Having in mind its track record in the intermolecular version of this reaction,[13] we chose the oxazoline group as the electron-withdrawing substituent.

Treating oxazoline **16** with MeLi/TMEDA gave organolithium **17**,[14] which cyclized even at −78 °C (Scheme 3).

Scheme 3. Dearomatizing Annelation of a Tetrahydrofuran[a]



[a] (i) MeLi, THF, TMEDA, −78 °C; (ii) −78 °C, 1 h; (iii) electrophile E^+ (see Table 1), −78 °C.

Trapping **18** with alkylating agents and other electrophiles yielded **19** in good yield (Table 1).[15] The products **19**, which contain the 6,6,5-ring system present in several of the important biologically active arylnaphthalene lignans,[16] are acid-sensitive compounds, unstable in $CDCl_3$, though they survive several days in benzene at room temperature.

Table 1. Cyclization of **16**

entry	E^+	E =	yield (%)	**19a**:**19b**[a]
1	NH_4Cl	H	74	>25:1
2	MeI	Me	79	>25:1
3	BnBr	Bn	75	3:1
4	PhCHO	PhCHOH	41[b]	>25:1[c]

[a] Ratio determined by ^1H NMR. [b] Yield of major epimer. [c] 3:2 ratio at hydroxyl-bearing center.

In most cases the cyclization−electrophilic quench sequence gave a single diastereoisomer (by ^1H NMR) on protonation or methylation. A large coupling (J = 15 Hz)

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(7) Dixon, J. A.; Fishman, D. H.; Dudinyak, R. S. *Tetrahedron Lett.* **1964**, 613.

(8) This solvent system avoids the formation of radicals during the iodine−lithium exchange; see: Bailey, W. F.; Patricia, J. J. *J. Organomet. Chem.* **1988**, *352*, 1.

(9) TMEDA assists the more reluctant anionic cyclisations; see ref 1.

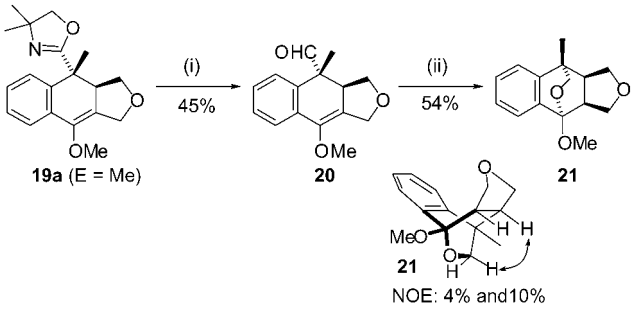
(10) Byproducts arising from anionic cyclization to an aromatic ring followed by rearomatization have previously been reported; see: Klumpp, G. W.; Schmitz, R. F. *Tetrahedron Lett.* **1974**, *15*, 2911. Krief, A.; Kenda, B.; Barbeaux, P.; Guittet, E. *Tetrahedron* **1994**, *50*, 7177.

(11) Nakai, T.; Mikami, K. *Org. React.* **1994**, *46*, 105. For comparable [2,3]-Wittig rearrangements involving aromatic double bonds, see: Tomooka, K.; Harada, M.; Hanji, T.; Nakai, T. *Chem. Lett.* **2000**, 1394. Garbi, A.; Allain, L.; Chokrki, F.; Crousse, B.; Bonnet-Delpon, D.; Nakai, T.; Bégué, J.-P. *Org. Lett.* **2001**, *3*, 2529.

between protons at the saturated carbons of the dearomatized ring of protonated product **19a** (E = H) suggests that they lie *trans* and hence indicates *endo*-protonation of **18**. Alkylation with MeI gave a single diastereoisomer of the product, while benzyl bromide gave an inseparable 3:1 mixture of diastereoisomers. Benzaldehyde reacted diastereoselectively at the new stereogenic center in the ring but gave a 3:2 mixture of epimers at the new hydroxyl-bearing center of alcohol **19a** (E = PhCHOH).

The stereochemistry of the alkylated products was assigned by NOE of **21**, a derivative of **19a** (E = Me). The oxazoline ring of **19a** (E = Me) was reduced[17] to a hydroxyl group via aldehyde **20**, and treatment with acid gave the acetal **21**. Clear NOEs (Scheme 4) in this tetracycle indicated *endo* stereoselectivity in the alkylation of **18**.

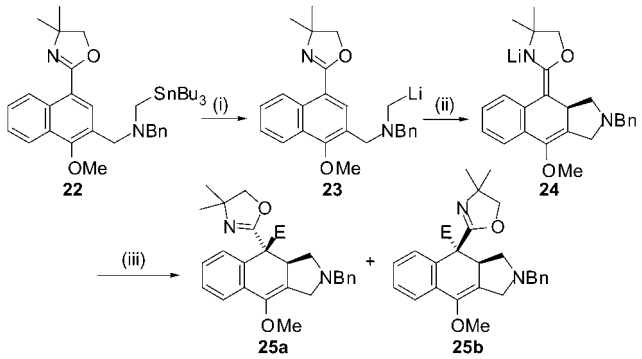
Scheme 4. Transformations and Stereochemistry[a]



[a] (i) (1) MeOTf, (2) $NaBH_4$, (3) $(CO_2H)_2$; (ii) (1) $NaBH_4$, (2) CF_3CO_2H.

Variation of the organolithium "tether" allowed us to annelate other saturated five-membered rings to the naphthalene system. For example, although the amino-substituted stannane **22** proved more resistant to tin−lithium exchange than **16**, warming to −40 °C with MeLi and TMEDA led to the formation of **23**. Cyclization to **24** occurred at this temperature, and **24** was trapped with electrophiles (Scheme 5 and Table 2) to yield tricyclic amines **25**.

Scheme 5. Dearomatizing Annelation of a Pyrrolidine[a]



[a] (i) MeLi, THF, TMEDA, −40 °C; (ii) −40 °C, 1 h; (iii) electrophile E^+ (see Table 2), −78 °C.

Table 2. Cyclization of **22**

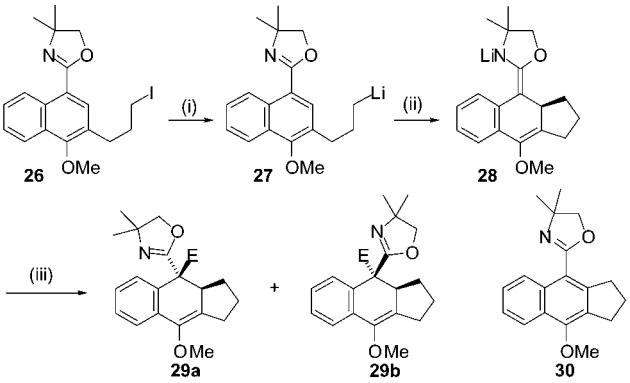
entry	E^+	E =	yield (%)	**25a**:**25b**[a]
1	NH_4Cl	H	73	>25:1
2	MeI	Me	71	>25:1
3	BnBr	Bn	13[b]	>25:1
4	allyl-Br	$CH_2CH{=}CH_2$	57	>25:1
5	PhCHO	PhCHOH	80	>25:1[c]

[a] Ratio determined by ^1H NMR; stereochemistry by analogy with **19**. [b] Low yield due to quaternization. [c] 3:2 ratio at hydroxyl-bearing center.

The diastereoselectivity of the cyclization and alkylation to give **25a** was even higher than in the formation of **19a**. A single diastereoisomer was obtained in every case (though again benzaldehyde gave a 3:2 mixture of epimers at the hydroxyl-bearing center). No rearomatized products were obtained on cyclization of **16** or **22**.

Products resulting from annelating a cyclopentane ring to a naphthalene skeleton were obtained by iodine−lithium exchange of **26** (Scheme 6). *t*-BuLi in THF at −78 °C gave

Scheme 6. Dearomatizing Annelation of a Cyclopentane[a]



[a] (i) *t*-BuLi (2.1 equiv), THF, −78 °C; (ii) −78 °C, 1 h; (iii) electrophile E^+ (see Table 3), −78 → 20 °C.

27, which cyclized to give **28** and resulted in good yields of single diastereoisomers (in most cases, to the limit of NMR detection) on reaction with electrophiles (Table 3).[18]

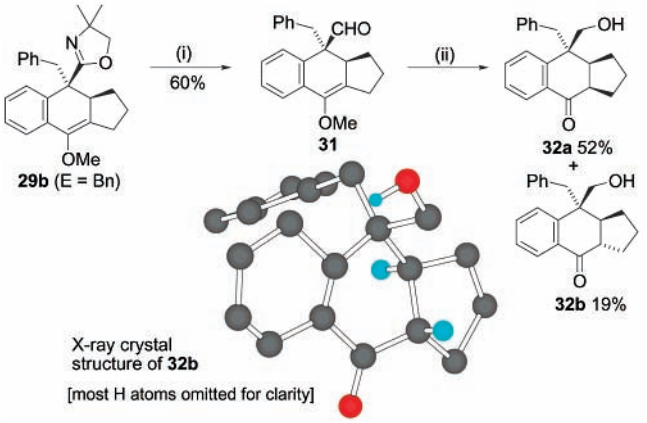
Table 3. Cyclization of **26**

entry	E^+	E =	yield (%)	**29a**:**29b**[a]
1	NH_4Cl	H	85	>25:1
2	MeI	Me	71	<1:25
3	BnBr	Bn	65	<1:25
4	allyl-Br	$CH_2CH{=}CH_2$	67	1:1
5	PhCHO	PhCHOH	45[b]	<1:25[c]

[a] Ratio by ^1H NMR. [b] Yield of major epimer. [c] 3:1 ratio at hydroxyl-bearing center.

Oxazoline **29b** (E = Bn) was reduced to aldehyde **31** (Scheme 7). Further reduction and hydrolysis of the enol

Scheme 7. Transformations and Stereochemistry

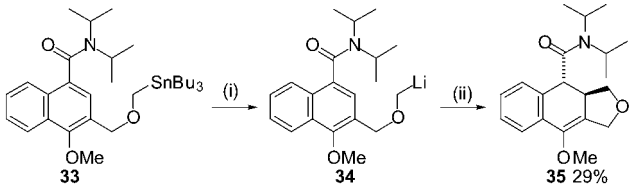


(i) (1) MeOTf, (2) $NaBH_4$, (3) $(CO_2H)_2$; (ii) (1) $NaBH_4$, (2) CF_3CO_2H.

ether gave, in contrast with aldehyde **20**, the hydroxyketones **32a** and **32b** (epimers α to the ketone) with no acetal analogous to **21**. An X-ray crystal structure of **32b** proved that **28**, in contrast with **18**, is alkylated from the *exo* face.[19]

Alternative carboxylic acid derived electron-withdrawing groups performed less well in the cyclization reactions. For example, the *N*,*N*-diisopropylamide **33** gave an organolithium that cyclized in poor yield to give an amide enolate that could be protonated though not alkylated (Scheme 8).

Scheme 8. Cyclization onto an Amido Naphthalene[a]

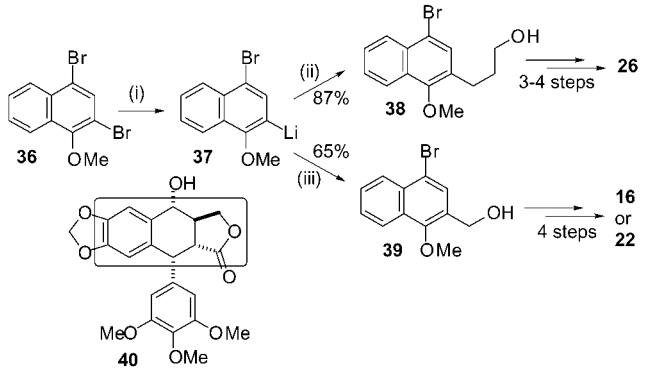


[a] (i) MeLi, THF, TMEDA, −78 °C; (ii) (1) −78 °C, 1 h, (2) NH_4Cl.

The potential of these methods for annelating rings to naphthalenes stems in part from the ease of synthesis of the starting materials. A general route is shown in Scheme 9. Treatment of 2,4-dibromo-1-methoxynaphthalene **36** with BuLi in Et_2O differentiates the bromo substituents through the action of the directing effect of the methoxy group.[20] We found that aryllithiums such as 2-lithionaphthalene and **37** react well with oxetane to give γ-hydroxypropylarenes such as **38**,[21] which can be converted to **26** in three to four steps. Alternatively, reaction of **37** with DMF followed by reduction gives **39**, which gives **16** or **22** in four steps.

The tetrahydrofurans **19**−**21** share structural features with biologically active arylnaphththalene lignans such as podophyllotoxin **40**.[16] We are currently investigating applications of dearomatizing cyclizations of this type to the synthesis of this class of compounds.

Scheme 9. Starting Materials and Targets[a]



[a] (i) BuLi, Et_2O, −78 °C; (ii) oxetane, BF_3; (iii) (1) Me_2NCHO, (2) $NaBH_4$.

Acknowledgment. We are grateful to the EPSRC and to BASF Pharma for support through a CASE award (to M.N.K.) and to Dr. Madeleine Helliwell for determining the X-ray crystal structure of **32b**.

Supporting Information Available: Experimental procedures for dearomatizing cyclizations, characterization data for key compounds **19a** (E = H), **25a** (E = Me), and **29a** (E = Bn), and crystallographic data for **32b** (in CIF format). This material is available free of charge via the Internet at http://pubs.acs.org.

OL0172626

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(15) Yields were lower without TMEDA.

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(18) Rearomatization of the dearomatized azaenolate intermediate gave traces (<5%) of aromatic byproduct **30**.

(19) The reason for the change from *endo* to *exo* selectivity in the alkylation associated with the change from a tetrahydrofuran to a cyclopentane annelation is not yet clear. The assignment of stereochemistry to the other compounds **29** is not confirmed.

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