ORGANIC LETTERS

2005
Vol. 7, No. 1
31−34

A New Chiral Anthracene for the Asymmetric Diels–Alder/ Retro-Diels–Alder Sequence

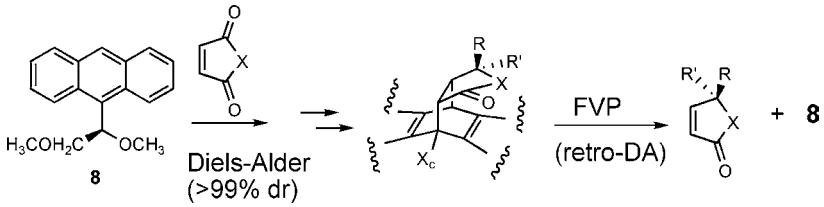
Kerrie L. Burgess, Neil J. Lajkiewicz, Amitav Sanyal, Wanlin Yan, and John K. Snyder*

Boston University, Department of Chemistry, Boston, Massachusetts 02215

jsnyder@chem.bu.edu

Received October 4, 2004

ABSTRACT



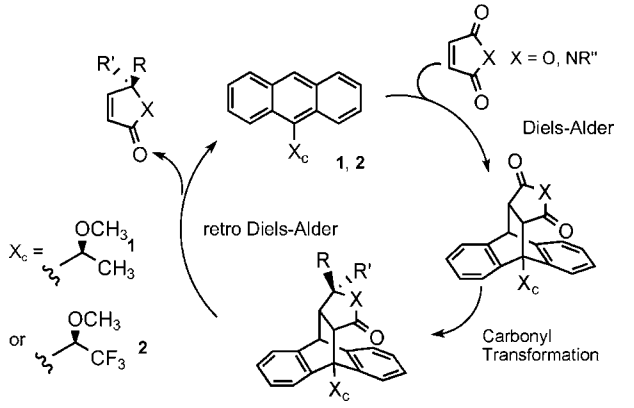
(–)-(*R*)-9-(1,2-Dimethoxyethyl)anthracene (8) is successfully employed as a chiral template in the Diels–Alder/retro-Diels–Alder sequence for the preparation of α,β-unsaturated lactams. The cycloadditions proceed with complete diastereoselectivity, and regioselectivity in subsequent transformations of the carbonyl groups is also excellent. Flash vacuum pyrolysis accomplishes the cycloreversion.

Butenolides and α,β-unsaturated γ-lactams are well-known pharmacophores that have evoked considerable effort in the development of new synthetic methodologies. We have been interested in developing a general synthetic route that could be easily amenable to these compound classes in enantiopure form and also be readily adaptable to library synthesis. To this end, a Diels−Alder/retro-Diels−Alder sequence employing a homochiral anthracene template, which would be recovered after the cycloreversion, as the stereocontrolling element seemed attractive (Scheme 1).

In an earlier report, 9-(1-methoxyethyl)anthracene (**1**) and 9-(1-methoxy-2,2,2-trifluoroethyl)anthracene (**2**) were used as chiral, nonracemic anthracenes in highly diastereoselective cycloadditions with maleic anhydride and *N*-methylmaleimide.[1] Jones subsequently demonstrated excellent stereoselectivity in the photochemically induced cycloadditions of **1**[2] and has also shown that the stereoselectivity can also operate under chelation control using the corresponding alcohol under appropriate conditions.[3] While these cycloadditions were very successful, **1** was prone to oxidation upon prolonged benchtop storage, while the reduced reactivity of **2** in cycloadditions with less reactive dienophiles was somewhat disappointing.

In an effort to improve the reactivity of the chiral anthracene template without compromising its stability, (*R*)-9-(1-methoxy-2,2,2-trifluoroethyl)-10-methylanthracene (**4**)

Scheme 1



(1) Sanyal, A.; Snyder, J. K. *Org. Lett.* **2000**, *2*, 2527.
(2) (a) Jones, S.; Atherton, J. C. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1117. (b) Atherton, J. C. C.; Jones, S. *J. Chem. Soc., Perkins Trans. 1* **2002**, 2166.

10.1021/ol047968a CCC: $30.25 © 2005 American Chemical Society
Published on Web 12/15/2004

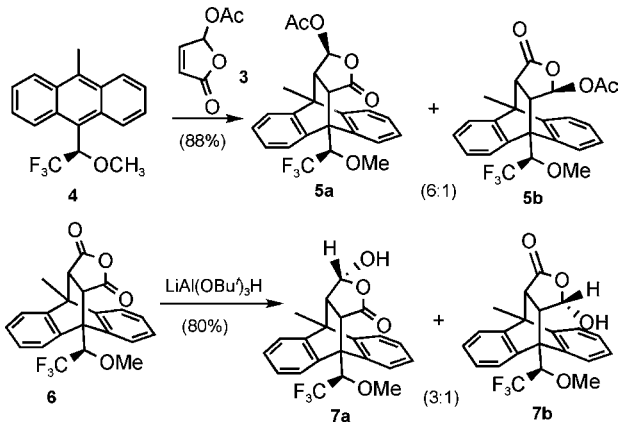
Table 1. Cycloadditions of **8** with Maleic Anhydrides and Maleimides (Scheme 3)

item	dienophile (eq)	cycloadduct	conditions	yield[a], d.e.
1	1.2 eq	**9a** (R = H)	C_6H_6 reflux, 9 h	90%, 99+% de
2	4 eq	**9b** (R = Br)	tol 110 °C,[b] 24 h	99%, 99+% de
3	4 eq	**9c** (Me)	tol 110 °C,[b] 48 h	99%, 99+% de
4	1 eq	**9d** (R = H)	C_6H_6, 85 °C,[b] 24 h	97%, 99+% de
5	1.8 eq	**9e** (R = Br)	C_6H_6, 85 °C,[b] 24 h	99+%/99+% de
6	1.7 eq	**9f** (n = 0)	C_6H_6, reflux, 24 h	99+%, 99+% de
7	1.1 eq	**9g** (n = 1)	MeOH, 80 °C,[b] 24 h	99%, 99+% de
8	2 eq	**9h** (n = 2)	C_6H_6, reflux, 24 h	97%, 99+% de

[a] Isolated yields. [b] Reactions were run in a sealed tube.

was prepared and examined in cycloadditions with maleate-derived dienophiles.[4] While **4** proved to be more reactive than **2**, yet retained the good benchtop stability exhibited by **2**, the regioselectivity in cycloadditions with nonsymmetric dienophiles such as **3a** was unfortunately compromised, giving only a 6:1 mixture of cycloadducts **5a** and **5b** (Scheme 2, eq 1). Furthermore, the regioselectivity in carbonyl

Scheme 2

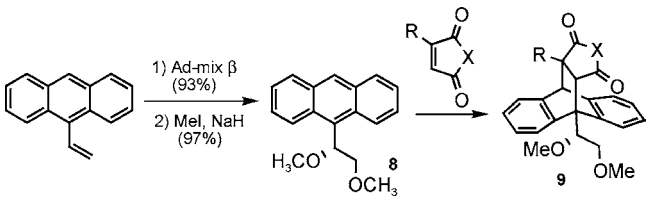


reductions of the maleic anhydride cycloadduct **6** could only be optimized to 3:1 (Scheme 2, eq 2).[5]

We have continued the search for better chiral anthracene templates that (1) retain good benchtop stability, (2) are at least as reactive as anthracene in cycloadditions, (3) show exclusive diastereoselectivity in the cycloadditions with dienophiles such as maleic anhydrides and maleimides, and (4) show excellent regioselectivity in carbonyl transformations of its cycloadducts. We now report that 9-(1,2-dimethoxyethyl)anthracene (**8**) meets these requirements and can be applied to a Diels−Alder/retro-Diels−Alder asymmetric synthetic sequence.

Adapting Corey's procedure,[6] 9-vinylanthracene was dihydroxylated with AD-mix-β to give the (*R*)-diol (93% on a 4 g scale), which was dimethylated (CH_3I/NaH, 97%) to produce **8** (Scheme 3). Chiral HPLC established the ee of **8**

Scheme 3



as 99+%. Anthracene **8** underwent cycloadditions with maleic anhydrides and maleimides to produce single diastereomers **9** in excellent yields (Table 1). Unsymmetric dienophiles such as bromomaleic anhydride, citraconic anhydride, and *N*-methyl-2-bromomaleimide produced solely the regioisomer with the original dienophile C2 substituent (Br or Me) remote to the original anthracene C9 stereogenic substituent (entries 2, 3, and 5).

With the cycloadducts in hand, work then focused on transformations of the succinimide subunits mounted on the

(3) Atherton, J. C. C.; Jones, S. *Tetrahedron Lett.* **2001**, *42*, 8239.
(4) Corbett, M. S.; Liu, X.; Sanyal, A.; Snyder, J. K. *Tetrahedron Lett.* **2003**, *44*, 931.
(5) Sanyal, A. Ph.D. Dissertation, Boston University, 2002.
(6) Corey, E. J.; Noe, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 11038.

Table 2. Carbonyl Transforms of Mounted Maleimides **9** through FVP (Schemes 4 and 5)[a]

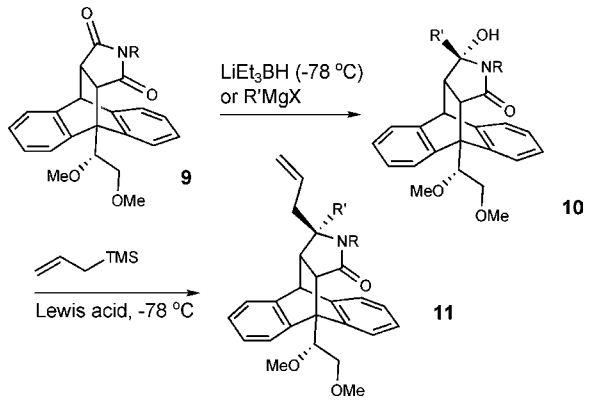
item/**9**	R	R′	yield/**10**[b] (%)	yield/**11**[c] (%)	yield/**12**[f] (%)	yield/**13**[g] (%)
1/**9d**	CH_3	Ph	96/**10a**	91[d]/**11a**	NA[h]	NA[h]
2/**9d**	CH_3	CH_3	83/**10b**	73[d]/**11b**	NA[h]	NA[h]
3/**9f**	$-CH{=}CH_2$	H	80/**10c**	0		
4/**9g**	$-CH_2CH{=}CH_2$	H	99+/**10d**	94[d]/**11d**	87/**12d**	60/**13d**
5/**9g**	$-CH_2CH{=}CH_2$	CH_3	99+/**10e**	77[d]/**11e**	99/**12e**	75/**13e**
6/**9g**	$-CH_2CH{=}CH_2$	Ph	98/**10f**	89[d]/**11f**	72/**12f**	60/**13f**
7/**9h**	$-CH_2CH_2CH{=}CH_2$	H	99+/**10g**	77[e]/**11g**	84/**12g**	50/**13g**
8/**9h**	$-CH_2CH_2CH{=}CH_2$	CH_3	99+/**10h**	72[e]/**11h**	99/**12h**	77/**13h**

[a] Isolated yields. [b] Grignard addition or Superhydride reduction. [c] Allylation with trimethylallylsilane. [d] $TiCl_4$, −78 °C to rt in CH_2Cl_2. [e] BF_3OEt_2, −78 °C to rt in CH_2Cl_2. [f] Ring-closing metathesis and hydrogenation, two steps. [g] FVP. [h] NA = not applicable/attempted.

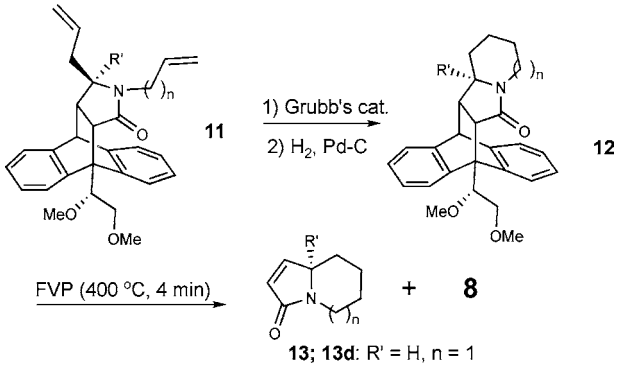
chiral anthracene template. Regioselective reactivity of the carbonyl groups in the cycloadducts **9** is critical to the use of the Diels−Alder/retro-Diels−Alder sequence in enantioselective synthesis since the lack of regioselectivity results in the production of enantiomers following cycloreversion. Selectivity in reductions and reactions with Grignard reagents was probed.

Superhydride ($LiEt_3BH$) reductions resulted in the regiochemically clean production of lactams **10c**, **10d**, and **10g** from **9f**, **9g**, and **9h**, respectively, with hydride addition occurring solely at the carbonyl remote to the original anthracene C9 stereocontrolling substituent (Scheme 4, Table 2, entries 3, 4, and 7). Grignard additions to the cycloadducts **9d**, **9g**, and **9h** (entries 1, 2, 5, 6, and 8) also occurred solely at this remote carbonyl. Presumably, evolving steric interactions between the anthracenyl stereogenic center and the developing sp^3 hybridization of the near carbonyl during nucleophilic addition increases the transition-state energy sufficiently to deny the alternative regiochemical outcome. Addition occurred solely from the top side of the imide, the anthracene template blocking approach from the bottom face. The regio- and stereochemistry of these additions was established by the observed coupling patterns and NOEs.[7] Subsequent allylation then produced the lactams **11** with the diene subunits suitably poised for ring-closing metathesis (RCM) in the cases of the *N*-allylmaleimide and *N*-butenylmaleimide adducts derived from **9g** and **9h**; allylation failed for **10c**. The RCM was routinely accomplished in excellent yields followed by hydrogenation to produce the desired indolizidine and the corresponding seven-membered ring homologue mounted on the anthracene template **12** ($n = 1$, 2, Scheme 5). Flash vacuum pyrolysis (400 °C, 4 min) then yielded the targeted bicycles **13** along with complete recovery of **8** (Table 2, last column). The bicyclic systems **13** with methine carbons at the ring fusion center (**13**, R′ = H) were not stable to prolonged storage.[8] This strategy to prepare the indolizidine bicyclic alkaloidal ring system as well as higher homologues by ring-closing metathesis of the larger ring parallels earlier approaches by Martin[9] as well as Hanessian.[10]

Scheme 4



Scheme 5



Resubjecting cycloadduct **9a** to the original cycloaddition conditions in both methanol and toluene in the presence of *N*-methylmaleimide led only to fully recovered **9a**; no crossover product was detected. A competition experiment between maleic anhydride and *N*-methylmaleimide in the cycloaddition with **8** revealed both cycloadducts were formed

(7) See the Supporting Information, **11a**, for details.

(8) Watson, R T.; Gore, V. K.; Chandupatla, K. R.; Dieter, R. K.; Snyder, J. P. *J. Org. Chem.* **2004**, *69*, 6105.

(9) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Paetzel, M.; Ramser, M. N. Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.

(10) Hanessian, S.; Sailes, H.; Munro, A.; Therrien, E. *J. Org. Chem.* **2003**, *68*, 7219.

(1:3.3, **9a**/**9d**). Thus, if the formation of **9a** was reversible under these conditions, crossover product would certainly have been detected, and the stereoselectivity was thus established to be under kinetic control.

The absolute stereochemistry of **13d** was established by comparison of its optical rotation with that reported in the literature,[11] which also allowed for the assignment of the absolute stereochemistry of **9g** and the remaining cycloadducts by analogy. This stereochemistry suggests a transition state for the cycloaddition wherein the methoxymethyl group is oriented antiperiplanar to the approaching dienophile with facial selectivity established through minimization of electrostatic repulsions between the auxiliary C9 methoxyl group and the dienophile carbonyl oxygens (Figure 1). Such an approach also minimizes steric interactions.

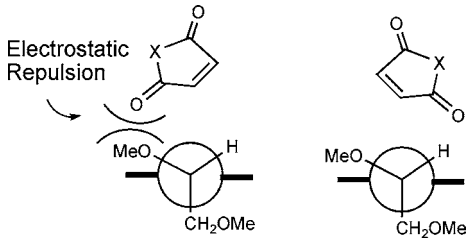
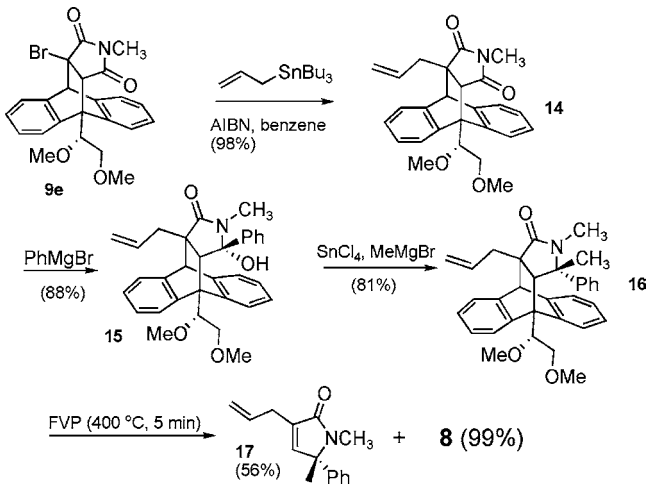


Figure 1. Proposed transition state to account for observed stereoselectivity in cycloadditions of **8**.

Cycloadduct **14** from the reaction of anthracene **8** with *N*-methyl-2-bromoaleimide, followed by near-quantitative radical allylation, was also subjected to Grignard addition (Scheme 6). In this case, phenyl Grignard addition occurred at the carbonyl remote to the allyl group and above the former anthracene C9 stereogenic center, presumably for steric reasons. A second Grignard addition to the in situ generated acyl iminium ion produced the γ,γ-disubstituted lactam **16**, which also underwent cycloreversion via flash vacuum pyrolysis to produce α,β-unsaturated lactam **17**. Thus, excellent regioselectivity was still observed with the C2-disubstituted succinimide **14**, though in this case at the other carbonyl group in comparison to the maleimide cycloadducts illustrated in Scheme 4 and Table 2.

(11) Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001** *66*, 5438.

Scheme 6



In conclusion, a new chiral anthracene template **8**, with excellent benchtop stability, has been prepared for use as the stereocontrolling element in a cycloaddition/cycloreversion sequence for the asymmetric synthesis of α,β-unsaturated γ-lactams. Only single stereoisomers were produced in the cycloadditions with maleimides and maleic anhydrides, and only single regioisomers were formed in the carbonyl transformations of the mounted dienophiles. Competition experiments using maleic anhydride as the dienophile revealed that **8** is 2.8 times more reactive than anthracene. Flash vacuum pyrolysis releases the transformed dienophile. Work continues to probe the scope of the cycloadditions of **8** with other dienophiles, as well as to investigate further transformations of the cycloadducts.

Acknowledgment. We thank the donors of the Petroleum Research Fund (ACS-PRF 35222-AC) for financial support and the Boston University Undergraduate Research Opportunity Program (UROP) for support of K.L.B. and N.J.L.

Supporting Information Available: Experimental procedures and characterization data including spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL047968A