ORGANIC LETTERS

2005
Vol. 7, No. 7
1335−1338

aza-Prins-pinacol Approach to 7-Azabicyclo[2.2.1]heptanes and Ring Expansion to [3.2.1]Tropanes

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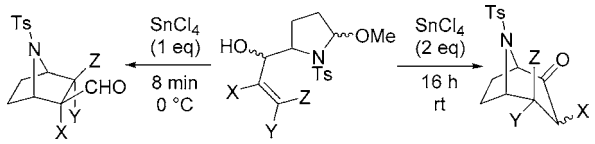
Received January 20, 2005

ABSTRACT



The 7-azabicyclo[2.2.1]heptane ring system can be rapidly accessed from 5-(1-hydroxyallyl)-2-alkoxy-*N*-tosylpyrrolidines via an unusual *aza*-Prins-pinacol reaction mediated by Lewis acid. The products can undergo ring expansion to isomeric tropanones. These reactions show promise for a concise entry to biologically relevant azabicyclic targets.

Nitrogen-bridged bicyclic ring systems have a long association with natural product chemistry and pharmaceutical products.[1] The tropane nucleus (Figure 1) is common to both

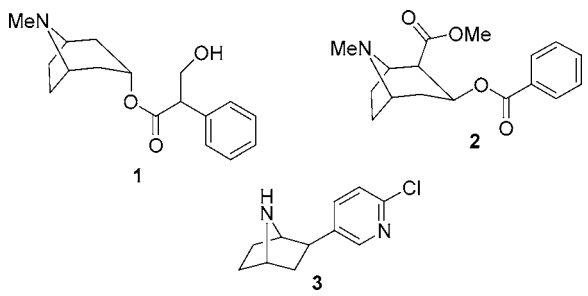
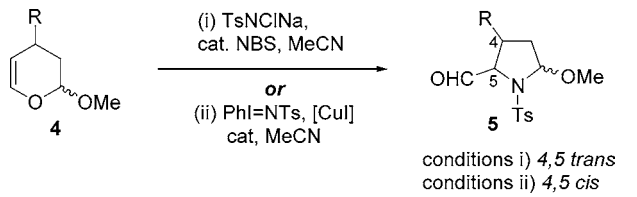


Figure 1.

atropine **1** and cocaine **2** and continues to be exploited today.[2] By contrast, interest in the 7-azabicyclo[2.2.1]heptane skeleton has increased considerably since the structural elucidation of the analgesic natural product epibatidine **3** in 1992.[3] Numerous syntheses of epibatidine and analogues have been reported,[4] although these are rarely suitable for the preparation of diverse analogues. An exception is the reductive Heck coupling strategy reported by Regan.[5] However, this is most suited to varying the pyridyl fragment.

We recently reported[6] that aminative rearrangement of alkoxydihydropyrans **4** gives facile access to pyrrolidines **5** (Scheme 1). The method is attractive because the substrates

Scheme 1



conditions i) *4,5 trans*
conditions ii) *4,5 cis*

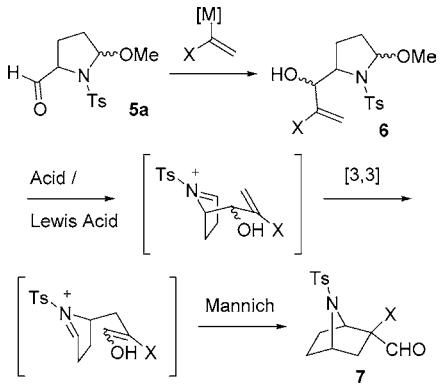
4 can be readily accessed via inverse electron demand [4 + 2] cycloaddition between an enol ether and an enone.

(1) Silverman, R. B. *The Organic Chemistry of Drug Design and Drug Action*; Academic Press: San Diego, 1992; p 2.
(2) Langlois, M.; Fischmeister, R. *J. Med. Chem.* **2003**, *46*, 319−344.
(3) Spande, T. F.; Garraffo, H. M.; Edwards, M. W.; Yeh, H. J. C.; Pannell, L.; Daly, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478.

10.1021/ol0501267 CCC: $30.25 © 2005 American Chemical Society
Published on Web 03/05/2005

Additionally, where a substituent R is present, we have demonstrated that the C4−C5 relative configuration of the product can be predictably controlled by the choice of appropriate aziridination conditions.[6] Compounds **5** are potentially bifunctional electrophiles: as well as containing a carbonyl group, they are precursors to *N*-sulfonyl iminium ions, which are competent electrophilic species.[7] We sought to exploit the bifunctional nature of pyrrolidines **5** in synthetic applications. We conceived that addition of vinyl organometallic reagents to the aldehyde group in **5a** should give access to allylic alcohols **6** (Scheme 2). Subsequent acidic

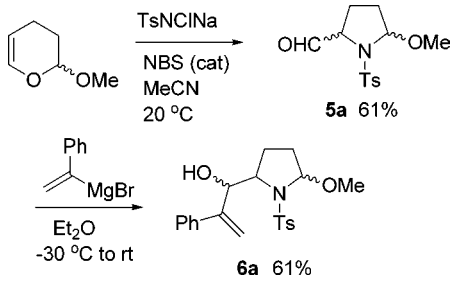
Scheme 2



activation of the masked *N*-sulfonyliminium function could be predicted to promote a novel variation on the *aza*-Cope−Mannich sequence pioneered by Overman.[8] The expected products would be 7-azabicyclo[2.2.1]heptanes **7**, the relative configuration of which was left as a question to address experimentally. This plan would constitute a flexible synthesis of the bicycle **7** from alkoxydihydropyrans **4** in only three chemical steps.

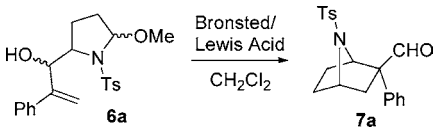
An initial test substrate **6a** was prepared, as a mixture of diastereoisomers, via reaction of pyrrolidine aldehyde **5a** with the Grignard reagent derived from α-bromo-styrene (Scheme 3). Several Bronsted and Lewis acids were screened (Table

Scheme 3



1), and gratifyingly $SnCl_4$ was found to bring about the desired transformation to azabicycloheptane **7a** in high yield. Only one diastereoisomer of **7a** was observed, possessing *endo* stereochemistry with respect to the phenyl group.

Table 1.

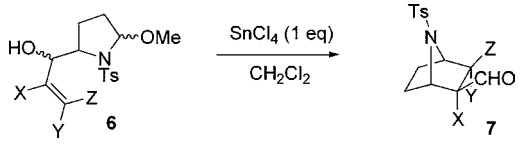


entry	acid	molar equiv	conditions	isolated yield of **7a** (%)
1	CSA[a]	0.08	80 °C, 16 h	0
2	$TiCl_4$	1	0 °C, 8 min	31
3	$Sc(OTf)_3$	0.1	25 °C, 17 h	0
4	$SnCl_4$	2	0 °C, 8 min	96
5	$SnCl_4$	1	0 °C, 8 min	96
6	$SnCl_4$	0.1	25 °C, 15 h	nd

[a] Acetonitrile solvent.

(Stereochemical configurations of compounds **7** were assigned on the basis of NOE studies and/or coupling constant data. See Supporting Information for details.) Optimization of the reaction identified preferred conditions (entry 5) employing 1 equiv of $SnCl_4$ at 0 °C for 8 min. Attempts toward a catalytic process with substoichiometric levels of $SnCl_4$ were unsuccessful (entry 6). At no time was the alternative *exo* stereoisomer observed. Interestingly, prolonged exposure to $SnCl_4$ was found to bring about the clean formation of unexpected alternative products. These were identified as isomeric tropanes **8a** and **9a** (Table 3, entry 1).

Table 2.



entry	substrate	X	Y	Z	time	temp (°C)	yield (%)
1	**6a**	Ph	H	H	8 min	0	96
2	**6b**	Me	H	H	8 min	0	81
3	**6c**	Me	H	Me	8 min	0	62
4	**6d**	Me	Me	H	8 min	0	61
5	**6e**	H	H	H	14.5 h	20	32
6	**6f**	SPh	H	H	1 min	0	11
7	**6g**	cyclohexenyl		H	8 min	0	0

By extension of the reaction time at ambient temperature, a high total yield (76%) of these [3.2.1]bicyclic compounds

(4) Representative examples: Broka, C. A. *Tetrahedron Lett.* **1993**, *34*, 3251−3254. Fletcher, S. R.; Baker, R.; Chambers, M. S.; Herbert, R. H.; Hobbs, S. C.; Thomas, S. R.; Verrier, H. M.; Watt, A. P.; Ball, R. G. *J. Org. Chem.* **1994**, *59*, 1771−1778.

(5) Clayton, S. C.; Regan, A. C. *Tetrahedron Lett.* **1993**, *34*, 7493−7496.

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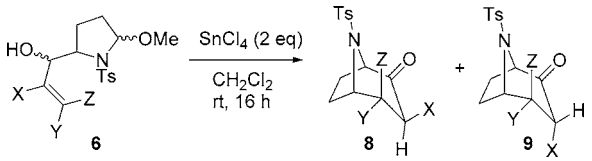
Table 3.

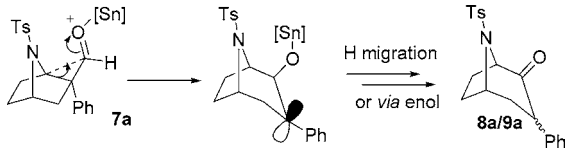


entry	substrate	yield **8** (%)	yield **9** (%)
1	**6a**	60	16
2	**6b**	37	17
3	**6c**	49	trace
4	**6d**	42	0
5	**6e**	0[a]	0

[a] No ring expansion observed after formation of **7e** as outlined in Table 2.

was obtained. **8a** and **9a** proved to be readily separable by chromatography. It was demonstrated that these tropanes arose via the intermediacy of azabicycloheptane **7a**: a pure sample of **7a** was resubjected to the reaction conditions and smoothly isomerized to the ring-expanded system. This novel interconversion of the two ring systems can be postulated to be mechanistically analogous (Scheme 4) to the recently

Scheme 4



observed carbocyclic variant reported by Davies et al.[9] The ca. 4:1 isolated ratio of **8a**:**9a** partly reflects epimerization during chromatography; the initial ratio according to NMR analysis of the crude reaction mixture was close to 1:1.

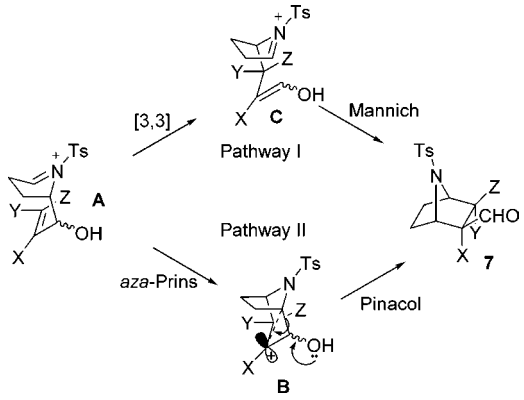
With preferred reaction conditions identified to access either the [2.2.1] or expanded [3.2.1] ring systems, we synthesized a range of alternative rearrangement precursors **6** (Tables 2 and 3). We hoped to probe the generality of the rearrangement and to shed further light on the mechanisms of conversion to products **7**−**9**. The strategy employed for preparation of **6b**−**g** was again addition of the appropriate vinyl Grignard reagent to aldehyde **5a**.

With respect to the formation of azabicycloheptanes **7** (Table 2), replacement of the phenyl vinyl substituent of **6a** with an aliphatic group (methyl) is well tolerated (entries 2−4). However, the presence of an unsubstituted vinyl group (entry 5) dramatically slowed the formation of **7e**. The low yield of **7f** from electron-rich vinyl compound **6f** (entry 6) is due to the rapid acceleration of ring expansion to unstable tropanes observed with this substrate, making halting the reaction at the azabicycloheptane stage difficult. For all substrates, only one diastereoisomer of **7** was observed, *exo* with respect to the aldehyde substituent, despite precursors **6** being diastereoisomeric mixtures. Substrates **6c** and **6d** (entries 3 and 4) demonstrate that the reaction is stereospecific with respect to olefin geometry in **6**, because they exclusively afforded products **7c** and **7d**, respectively. Substrate **6g**, possessing a cyclic alkenyl fragment, failed to rearrange, giving a complex product mixture (entry 7).

Formation of tropanes **8** or **9** (Table 3) was also tolerant of substituent X being changed from phenyl to methyl (entries 2−4). However, employing an unsubstituted vinyl group (entry 5) halted the reaction at azabicycloheptane **7e** as previously described. Given that ring expansion to tropanes **8/9** is observed to be a slower process than formation of **7**, this result is not altogether surprising in view of the already slow rate of azabicyclo[2.2.1]heptane formation observed with this substrate. Olefin geometrical isomers **6c** and **6d** again produced different isomeric tropane products (entries 3 and 4). This is the expected outcome of the proposed ring expansion mechanism for isomerization of **7** to **8/9** (Scheme 4): connectivity of the bicyclic ring system is maintained throughout, maintaining the syn or anti disposition of substituents Y/Z relative to the nitrogen bridge. (Proposed structures for **8c**, **9c**, and **8d** are corroborated by key spectral features. See Supporting Information for details.)

The complete diastereoselectivity and stereospecificity (with regard to alkene geometry) of formation of products **7** prompted us to consider alternative mechanistic explanations for their generation. Two pathways were prominent in our consideration (Scheme 5): an *aza*-Cope−Mannich process

Scheme 5

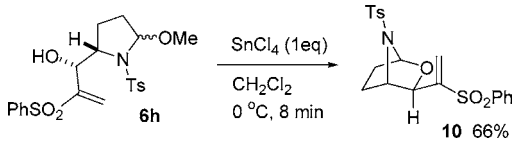


as originally planned (pathway I) and an *aza*-Prins-pinacol reaction (pathway II). In pathway II, the carbocation intermediate **B** must undergo rapid pinacol rearrangement to give the more strained [2.2.1]azabicycle **7** as the kinetic product; prolonged exposure to Lewis acid would lead to the thermodynamically more stable, less strained [3.2.1]-system **8**/**9** via reversion to **B** and H-migration/enol formation (cf. Scheme 4). In both pathways I and II, the observed *exo*

(8) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310. For a review, see: Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359.
(9) Davies, H. M. L.; Dai, X. *J. Am. Chem. Soc.* **2004**, *126*, 2692−2693. Niess, B.; Hoffmann, H. M. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 26−29.

orientation of substituent Z in compounds **7** requires a chairlike topography for whichever process consumes the intermediate iminium ion **A**. Overman and co-workers proposed that pathway I is generally operative for systems containing the more usual *N*-alkyl iminium ions.[10] They proposed that pathway II can occur for electronically biased substrates such as vinyl ethers[10] and showed that an analogous mechanism is the norm for the related Prins-pinacol reaction of oxonium ions.[11] Key evidence presented by Overman for pathway I is the observation that *aza*-Cope−Mannich reactions tolerate a sulfone vinyl substituent[10] (Scheme 5, substituent X). The formation of a carbocation α to a sulfone group X, required by pathway II, is unlikely.[12] As a test of mechanism and direct comparison with the work of Overman, we prepared sulfone **6h** and attempted its rearrangement under our preferred reaction conditions for the formation of azabicycloheptanes (Scheme 6). No rearrangement product was observed, the sulfonyl iminium intermediate merely being trapped by the alcohol function to give isolated product **10**. We therefore suggest that the formation of products **7** occurs via an *aza*-Prins-pinacol process (Scheme 5, pathway II). Similar argument around the need to form carbocationic intermediate **B** in an *aza*-Prins-pinacol process can explain the observed dramatic rate deceleration for substrate **6e** (Table 2, entry 5), where a secondary rather than tertiary carbocation would be invoked. The *aza*-Prins-pinacol mechanism is an attractive explanation for the formation of azabicycloheptanes **7**, since it readily explains the observed stereochemical configuration of the products and the lack of dependence on the configuration of substrates **6**. Should an *aza*-Cope-Mannich process operate (Scheme 5, pathway I), stereoconvergence to a single isomer of product **7** would require enol intermediate **C** to react exclusively in the conformation shown, regardless of its *E*/*Z* geometry. The pinacol process would be syn stereospecific, irrespective of the configuration at the alcohol stereocenter in carbocation intermediate **B** (Scheme 5, pathway II). Hence, a single isomer of product **7** (aldehyde *exo*) would be formed.

Scheme 6



In summary, we report the stereocontrolled formation of the 7-azabicyclo[2.2.1]heptane nucleus via an unusual *aza*-Prins-pinacol reaction. This mechanistic rationale is lent credence by both the influence of substrate electronics and the observed stereoselectivity and stereospecificity of the reaction. The aldehyde products can undergo a novel ring expansion to isomeric tropanes. Both ring systems are of considerable industrial importance and can be accessed concisely with multiple opportunities for structural diversity. The ready availability of the starting materials **4** bearing a wide range of substituents, including the possibility of accessing them in enantiomerically pure form using catalytic asymmetric hetero-Diels−Alder chemistry,[13] is a highly attractive feature. Synthetic applications of this methodology to natural product synthesis are under investigation in our laboratory.

Acknowledgment. We gratefully acknowledge support from the EPSRC (studentship for S.E.S.) and unrestricted funding from Bristol-Myers Squibb, Merck, and Pfizer.

Supporting Information Available: Full experimental and characterization for compounds **7**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0501267

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