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Exploiting the Ring Strain in Bicyclo[2.2.1]heptane Systems for the Stereoselective Preparation of Highly Functionalized Cyclopentene, Dihydrofuran, Pyrroline, and Pyrrolidine Scaffolds

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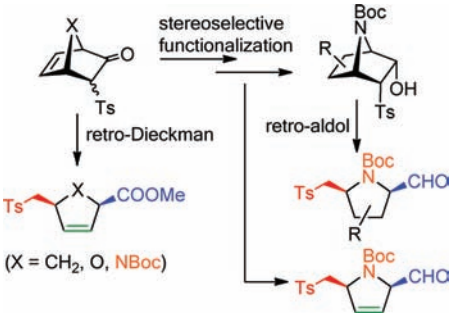
ABSTRACT



The high strain of bicyclic systems drives retro-condensation reactions on bridgehead substituted bicyclo[2.2.1]hept-2-enes giving rise to orthogonally functionalized cyclopentene, 2,5-dihydrofuran, and 3-pyrroline scaffolds. Retro-Dieckman reactions were easily carried out on 3-tosyl-(7-carba/7-oxa/7-aza)bicyclo[2.2.1]hept-5-en-2-ones. Retro-aldol reactions of *N*-Boc-3-tosyl-7-azabicyclo[2.2.1]hept-5-en-2-ol and functionalized *N*-Boc-3-tosyl-7-azabicyclo[2.2.1]heptan-2-ols yield functionalized pyrrolidine scaffolds stereoselectively. The same reaction does not work with corresponding norbornene and 7-oxanorbornene derivatives.

Five-membered rings, such as cyclopentane, tetrahydrofuran, and pyrrolidine derivatives, are widely found in natural products. In contrast to the situation with six-membered rings, five-membered rings usually do not adopt a single well-defined conformation. They exist as a rapidly interconverting mixture of envelope and twist conformations, which makes the stereoselective synthesis of functionalized cyclopentane, tetrahydrofuran, and pyrrolidine derivatives more difficult compared with the synthesis of corresponding six-membered analogues.

A common approach for the synthesis of diastereomerically pure substituted cyclopentanes is the use of conformationally rigid norbornene derivatives ([2.2.1]bicyclic systems) as precursors. The substituents can be introduced stereoselectively onto the rigid norbornene ring in an easy manner, so the cleavage of a suitable bond in the bicyclic skeleton should lead to cyclopentane derivatives with well-defined configurations. Important examples of this methodology are reported for cyclopentane derivatives.[1] One of them is the classical Corey's synthesis of prostaglandins.[2] On the other hand, a strategy based on the preparation of functionalized tetrahydrofurans (as rare carbohydrate analogues) from 7-oxabicyclo[2.2.1]hept-5-ene-2-yl derivatives was developed by Vogel's group with the so-called "naked sugar" methodology[3] and further extended to the preparation of hydroxylated pyrrolidine derivatives from

(1) For recent review, see: Heasley, B. *Eur. J. Org. Chem.* **2009**, 1477.
(2) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675. (b) Corey, E. J.; Schaaf, T. K.; Huber; Koelliker, W. U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397.

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7-azabicyclo[2.2.1]heptanes by the same research group ("aza-naked sugars").[4] Other transformations of azabicyclic systems into pyrrolidine and aminocyclohexene derivatives have also been recently reported,[5] including the interesting synthesis of *cis*-2,5-disubstituted pyrrolidine building blocks from 2-tropinone derivatives.[6]

All these strategies require the opening of the functionalized bicyclic skeleton through well established reaction sequences, such as ozonolysis and metathesis of double bonds, Baeyer–Villiger oxidation of bicyclic ketones, and subsequent lactone alcoholysis, among others. Norbornene is more strained (ca. 100 kJ/mol) than the sum of cyclopentene (23.4 kJ/mol) and cyclopentane (26.4 kJ/mol) which is comparable with those of cyclobutane and cyclopropane (111 and 115 kJ/mol, respectively).[7] The relatively high ring strain of bicyclo[2.2.1]hept-2-ene systems has been scarcely exploited for the construction of functionalized cyclopentene derivatives.[8]

In this paper we present a novel synthesis of functionalized cyclopentene, 2,5-dihydrofuran, 3-pyrroline, and pyrrolidine by ring opening on the appropriate strained bicyclic β-keto- and β-hydroxysulfone through reverse Dieckman and aldol reactions. In the case of 7-oxa- and 7-azanorbornenes with an electronegative atom bridge, the ring strain increases due to a shorter carbon–heteroatom bond. The highly functionalized five-membered ring systems constitute convenient scaffolds for organic and bioorganic chemistry.

We have previously reported that when crude racemic 7-azanorbornenone **1** was passed through a chromatography column (SiO_2, CH_2Cl_2–MeOH) for purification, the pyrroline byproduct **2** could be isolated (Figure 1).[9] Pyrroline **2** can be seen as a versatile scaffold for the preparation of unsymmetric 2,5-*cis*-disubstituted pyrrolidines, of which few synthetic routes have been reported.[6,10] The formation of **2** can be explained through a retro-Dieckman reaction on the β-ketosulfone induced by the high ring strain of the unsaturated bicyclic skeleton, increased in this case by the presence of the sp^2 carbon atom of the ketone group. However, the reproducibility of this opening reaction was difficult and strongly depended on the chromatographic conditions.

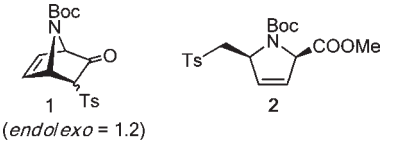


Figure 1. Previously described pyrroline **2** and 7-azanorborn-5-en-2-one **1**.

To accurately define the ring-opening experimental conditions and study the scope of this reaction, we have explored the methanolysis (formal retro-Claisen type reaction) of 7-azanorbornenone **1** and of its oxa- and carba-analogues, **7** and **8**, whose general synthesis is outlined in Scheme 1. We have also explored the ring opening of strained norborn-5-en-2-ol derivatives **9**–**11** through a retro-aldol reaction. Thus, 7-azanorbornadiene **4**, 7-oxanorbornadiene **5**, and norbornadiene **6** were prepared through a Diels–Alder reaction between *p*-tolyl-2-bromoethynylsulfone **3**[11] and the corresponding diene according to the procedure described by Trudell and co-workers,[12] including some experimental modifications in the case of **5** and **6**.[13] Treatment of **4**, **5**, and **6** with a mixture of triethylamine/diethylamine in acetonitrile followed by addition of 10% HCl afforded the known bicyclic ketone **1**,[9,12] and the new bicyclic ketones **7** and **8**, respectively, as mixtures of epimers. This step implies a three-reaction sequence: (i) conjugate addition of diethylamine to the vinyl sulfone, (ii) elimination of HBr promoted by the triethylamine to afford the enamine intermediate, (iii) acidic hydrolysis of the resulting enamine to give the ketone. In the case of norbornadiene **6**, the initial conjugate addition of diethylamine to the double bond was clearly slower than in the case of 7-aza and 7-oxa analogues **4** and **5**, respectively, requiring a higher temperature (50 °C) and a longer reaction time.

The stereoselective synthesis of azabicyclic alcohol **9** from ketone **1** was previously reported by us using $LiBH_4$ in THF at low temperature.[9] When the same reducing

(3) For example, see: (a) Warm, A.; Vogel, P. *J. Org. Chem.* **1986**, *51*, 5348. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173. (c) Vogel, P.; Sevin, A.-F.; Kernen, P.; Bialecki, M. *Pure Appl. Chem.* **1996**, *68*, 719. (d) Vogel, P.; Cossy, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521. (e) Vogel, P. *Curr. Org. Chem.* **2000**, *4*, 455. (f) Robina, I.; Vogel, P. *Synthesis* **2005**, 675. (g) Vogel, P. In *Organic Chemistry of Sugars*; Levy, D. E., Fügedi, P., Eds.; CRC LLC: Boca Raton, FL, 2006; p 629.

(4) For recent examples on the synthesis of functionalized pyrrolidines from 7-azanorbornanes, see: (a) Moreno-Vargas, A. J.; Vogel, P. *Tetrahedron Lett.* **2003**, *44*, 5069. (b) Moreno-Vargas, A. J.; Robina, I.; Petricci, E.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4487. (c) Ruggiu, A. A.; Lysek, R.; Moreno-Clavijo, E.; Moreno-Vargas, A. J.; Robina, I.; Vogel, P. *Tetrahedron* **2010**, *66*, 7309.

(5) (a) Kamimura, A.; Nakano, T. *J. Org. Chem.* **2010**, *75*, 3133. (b) Pandey, G.; Tiwari, K. N.; Puranik, V. G. *Org. Lett.* **2008**, *10*, 3611. (c) Bu1chert, M.; Meinke, S.; Prenzel, A. H. G. P.; Deppermann, N.; Maison, W. *Org. Lett.* **2006**, *8*, 5553.

(6) (a) Zhang, S.; Xu, L.; Miao, L.; Shu, H.; Trudell, M. L. *J. Org. Chem.* **2007**, *72*, 3133. (b) Shu, H.; Noble, A. R.; Zhang, S.; Miao, L.; Trudell, M. L. *Tetrahedron* **2010**, *66*, 4428.

(7) (a) North, M. In *Advances in Strained and Interesting Organic Molecules*; Halton, B., Ed.; JAI Press: Stamford, CN, 2000; Vol. 8, pp 145–185. (b) NIST Chemistry WebBook.

(8) For some recent examples, see: (a) Avenoza, A.; Barriobero, J. I.; Busto, J. H.; Peregrina, J. M. *J. Org. Chem.* **2003**, *68*, 2889. (b) Pellegrino, S.; Clerici, F.; Gelmi, M. L. *Tetrahedron* **2008**, *64*, 5657.

(9) Moreno-Vargas, A. J.; Schütz, C.; Scopelliti, R.; Vogel, P. *J. Org. Chem.* **2003**, *68*, 5632.

(10) For recent examples, see: (a) Wang, P.-A.; Xu, Z.-S.; Chen, C.-F.; Gao, X.-G.; Sun, X.-L.; Zhang, S.-Y. *Chirality* **2007**, *19*, 581. (b) Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 7297. (c) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C; Cowley, A. *Org. Lett.* **2003**, *5*, 999.

(11) Alkyne **3** can be easily obtained by bromination of commercially available *p*-tolyl 2-(trimethylsilyl)ethynyl sulfone, according to ref 12.

(12) Zhang, C.; Ballay, C. J., II; Trudell, M. L. *J. Chem. Soc., Perkin Trans. 1* **1999**, 675.

(13) The syntheses of 7-oxanorbornadiene and norbornadiene systems **5** and **6** were previously reported in ref 12. However, the experimental procedure was slightly modified with different temperatures and times for the cycloaddition reaction. Detailed experimental procedures and characterization data for **5** and **6** are given in this paper for the first time (see Supporting Information). The synthesis of the aza-analogue **4** was also previously described by us; see ref 9.

Scheme 1. General Synthesis of (7-Hetero)norborn-5-en-2-ones and (7-Hetero)norborn-5-en-2-ols

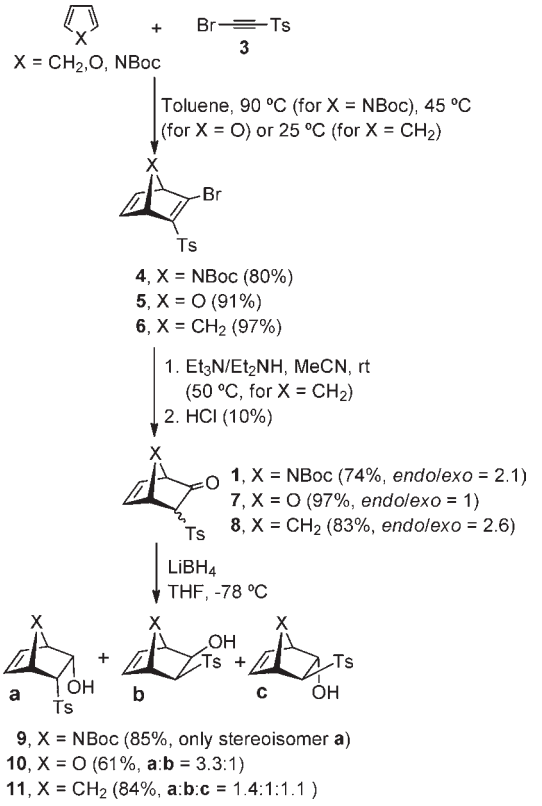
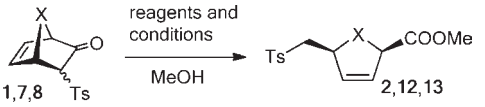


Table 1. Retro-Dieckman Reaction on (7-Hetero)norborn-5-en-2-ones



entry	X	reaction conditions	product	yield (%)
1	NBoc	AcOH (cat.), rt, 1 h	**2**	quant
2	NBoc	NaOMe (cat.), rt, 1 h	**2**	82
3	O	AcOH (cat.), rt, 1 h	**12**	quant
4	O	NaOMe (cat.), rt, 1 h	**12**	quant
5	CH_2	NaOMe (cat.), rt, 1 h	**13**[a]	quant[a]
6	CH_2	Py (1 equiv), rt, 1 h	**13**	quant
7	CH_2	AcOH (cat.), rt, 1 h	–	–[b]
8	CH_2	AcOH (1 equiv), rt, 24 h	–	–[b]
9	CH_2	TfOH (1 equiv), 60 °C, 72 h	–	–[b]

[a] Epimerization of C-2 in compound **13** was detected (1:1 ratio). [b] Starting material was recovered.

conditions were applied to the oxa- and carba-analogues, the reaction was not totally stereoselective and mixtures of stereoisomers were obtained: **10a** and **10b**, for the oxa-analogue, and **11a**, **11b** and **11c**, for the carba-analogue.

For azanorbornenone **1**, the retro-Dieckman reaction could be induced by a catalytic amount of AcOH in MeOH (Table 1, entry 1), affording the desired pyrroline **2** in a quantitative manner. Additionally, the treatment of **1** with a catalytic amount of NaOMe in MeOH afforded the same pyrroline (Table 1, entry 2) in excellent yield. These results were also obtained when the same reaction conditions were applied to the oxabicyclic ketone **7** to afford the new 2,5-dihydrofuran **12** in a very clean process (Table 1, entries 3 and 4). However, in the case of norbornenone **8**, the retro-Dieckman reaction only worked successfully when applying pyridine as a basic promoter. This led to the new cyclopentene **13** in quantitative yield.[14] The use of NaOMe in MeOH induced the ring opening of **8** but simultaneously provoked the epimerization of C-2 in **13**, even when a catalytic amount of the base was used. Under acidic conditions (AcOH or TfOH in a catalytic or stoichometric amount) no ring opening was observed.

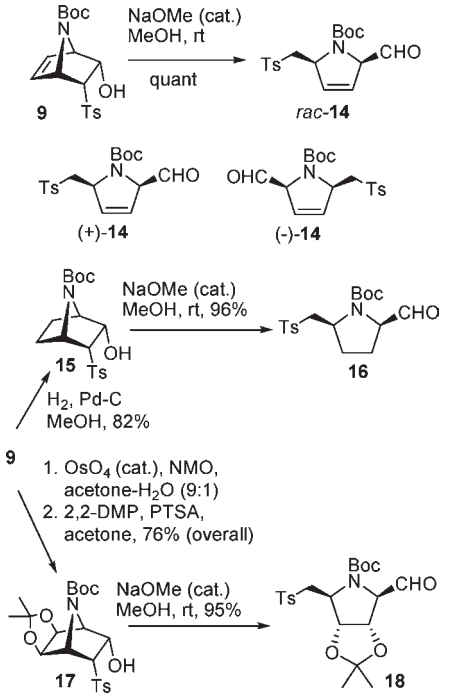
As the β-hydroxysulfone functionality is present in alcohols **9**–**11**, attempts to open these bicyclic systems through a retro-aldol reaction were carried out (Scheme 2).

The formyl pyrroline **14** was obtained by treatment of the azabicyclic alcohol **9** with NaOMe (cat.) in MeOH (2 h, rt). As racemic alcohol **9** can be easily resolved,[9] both enantiomerically pure aldehydes (−)-**14** and (+)-**14** were also prepared readily. The retro-aldol reaction was unsuccessful in the case of oxa- and carba-analogues **10** and **11**. None of these alcohols reacted when treated with NaOMe (cat.) in MeOH at room temperature. Attempts to increase the amount of NaOMe and/or the temperature of reaction led to complex mixtures of compounds together with unreacted starting materials. Probably, norbornenol derivatives **10** and **11** do not have enough strain to induce the retro-aldol reaction, in spite of the fact that norbornenes are more strained than cyclopentenes and cyclopentanes (the gas phase isomerization of cyclopentanol into pentanal is endothermic by only 10 kJ/mol). The high reactivity observed for the azabicyclic systems toward both reverse reactions could be explained by the presence of the Boc protecting group which induces an extra strain due to gauche effects in the bicyclic systems that is released upon ring opening and to the partially sp^2 hybridized 7-aza moiety of the carbamate group (7-methylidenenorbornane is more strained than 2-methylidenenorbornane by 8 kJ/mol).[15]

(14) Purification of compounds **2**, **12**, and **13** was not required after the opening reaction.

(15) Vogel, P. *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttgart-New York, 2005; Vol. 26, p 13.

Scheme 2. Retro-Aldol Reactions on 7-Azanorborn-5-en-2-ol and 7-Azanorbornan-2-ol Derivatives



In order to study the influence of the double bond in the retro-aldol opening reaction of the azabicyclic system, the preparation of the saturated azabicycle **15** was achieved by catalytic hydrogenation of **9** (Scheme 2). Retro-aldol opening of the saturated bicycle, under usual conditions, afforded the formyl pyrrolidine **16** in excellent yield. In this case, as expected, the ring-opening reaction was slower than in the case of the unsaturated analogue. Nevertheless, after 10 h all the starting material was transformed into the pyrrolidine derivative at room temperature. This observation showed that the presence of the double bond in this bicyclic system favors the ring opening due to a higher ring strain (by about 33 kJ/mol, between norbornene and norbornane)[7b] but is not critical for the reaction outcome. This result led us to attempt the retro-aldol opening on a highly functionalized system such as the hydroxylated bicycle **17**, previously obtained from **9** with total and unambiguous control of the stereoselectivity.[9] Treatment of **17** with NaOMe (cat.) in MeOH afforded the formyl pyrrolidine **18** after 1 h in a clean reaction. The rate of this reaction is comparable to the opening of the unsaturated derivative **9** and much faster than the opening of saturated azabicycle **15**, which indicates that the *exo*-5,6-(2,2-dimethyldioxolane) moiety induces a similar strain to the polycyclic system as does the endocyclic double bond. This might be attributed to extra gauche effects between the methyl group and the BocN moiety of **17**. Both enantiomers of pyrrolidine **18** can be easily prepared starting from enantiomerically pure alcohols **9** and *ent*-**9**.

To conclude, retro-Dieckman reactions of bicyclo[2.2.1]-hept-5-en-2-ones and retro-aldol reactions of bicyclo-[2.2.1]hept-5-en-2-ols permit the stereoselective synthesis of polyfunctional cyclopentene-, 2,5-dihydrofuran-, and 3-pyrroline-based scaffolds. The methodology has been extended to the functionalization of the double bond in 7-azabicyclo[2.2.1]hept-2-ene systems, allowing the additional installation of two functional groups in a stereoselective manner taking advantage of the high facial stereoselectivity and regioselectivity of the reactions of the norbornene double bond.[3] Ring opening of the polyfunctionalized azabicycles affords new pyrrolidine based scaffolds ideally suited for the construction of iminosugars (polyhydroxylated-pyrrolidines, indolizidines, and pyrrolizidines). The presence of aldehyde and $-CH_2Ts$ functions in pyrroline **14** and pyrrolidine **18** makes these compounds interesting precursors for further Wittig and Julia olefination reactions.

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Supporting Information Available. Experimental details and ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.