

trans-Acetonide Controlled *endo*-Selective Intramolecular Nitron–Alkene Cycloaddition of Hept-6-enoses: A Facile Entry to Calystegines, Tropanes, and Hydroxylated Aminocycloheptanes

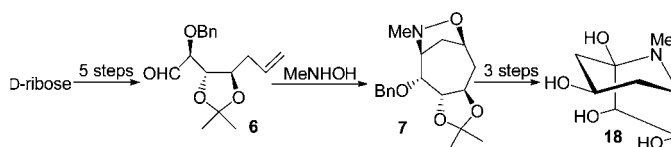
Tony K. M. Shing,^{*,†} Wai F. Wong,[†] Taketo Ikeno,[‡] and Tohru Yamada^{*,‡}

Department of Chemistry and Center of Novel Functional Molecules, The Chinese University of Hong Kong, Shatin, NT, Hong Kong, China, and Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi, Kohoku-ku, Yokohama, 223-8522, Japan

tonyshing@cuhk.edu.hk

Received October 25, 2006

ABSTRACT



High-yielding *endo*-selective intramolecular nitron–alkene cycloaddition (INAC) reactions of hept-6-enoses controlled by a *trans*-acetonide to give bridged bicyclo[4.2.1]isoxazolidines exclusively are realized for the first time. The cycloadducts were readily transformed into calystegine, tropane, and hydroxylated aminocycloheptane frameworks.

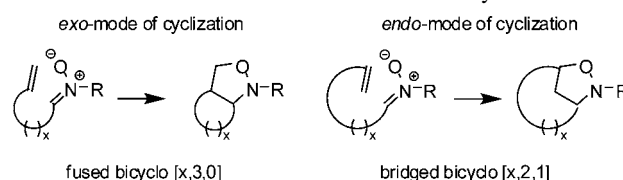
Intramolecular nitron–alkene cycloaddition (INAC) is a versatile and important synthetic method for the preparation of polyhydroxylated carbocycles from sugars.¹ The *exo* or the *endo* mode of INAC cyclization leads to a fused or a bridged isoxazolidine, respectively (Scheme 1).²

There are only two examples³ of the formation of a bridged bicyclo[4.2.1] system, i.e., a cycloheptane skeleton from branched sugars, but many examples¹ of unbranched hept-6-enose derivatives give a fused bicyclo[4.3.0] system, i.e.,

a cyclohexane skeleton. However, the regio- and diastereo-selectivity of these INAC reactions have not been rationalized.

The bridged bicyclo[4.2.1]isoxazolidine **1** is a versatile synthetic intermediate because, upon hydrogenolysis of the N–O bond, it provides the skeleton of aminocycloheptanol

Scheme 1. The Two Modes of INAC Cyclization



[†] The Chinese University of Hong Kong

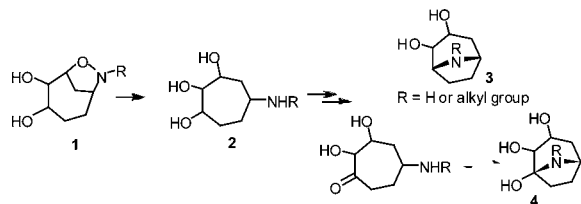
[‡] Keio University

(1) Koumbis, A. E.; Gallos, J. K. *Curr. Org. Chem.* **2003**, *7*, 585–628.
(2) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 83–168.

(3) (a) Roy, A.; Chakrabarty, K.; Dutta, P. K.; Bar, N. C.; Basu, N.; Achari, B.; Mandal, S. B. *J. Org. Chem.* **1999**, *64*, 2304–2309. (b) Patra, R.; Bar, N. C.; Roy, A.; Achari, B.; Ghoshal, N.; Mandal, S. B. *Tetrahedron* **1996**, *52*, 11265–11272.

2, proven to be a new class of glycosidase inhibitor.⁴ Synthetic manipulation of **2** could lead to alkaloid tropane **3**⁵ and calystegine **4**⁶ that exhibits specific glycosidase inhibition⁷ (Scheme 2). Optically active tropanes are still in

Scheme 2. Catalytic Hydrogenolysis of the N–O Bond in Isoxazolidine **1** and Subsequent Transformation



demand for neuroscience research⁸ and the chemotherapeutic use of glycosidase inhibitors as antitumor, antiviral, and antidiabetic agents has been recognized.⁹ Thus stereocontrolled *endo*-selective INAC reactions of hept-6-enoses to give bridged bicyclo[4.2.1]isoxazolidines are highly desirable. The present letter reports the use of *trans*-acetonide to effect such regioselectivity for the first time and the facile conversion of the cycloadducts into two calystegines **18** and **20**, one tropane **22**, and one hydroxylated aminocycloheptane **24**.

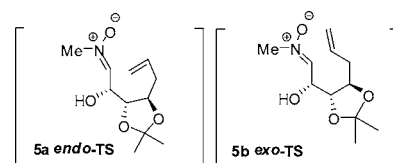
Recently, we reported¹⁰ that *exo*-INAC cyclization was the preferred pathway for hept-6-enoses containing a *cis*-acetonide to give fused isoxazolidine exclusively whereas hept-6-enoses with a 2,3-*O-trans*-diacetal gave a mixture of fused (cyclohexane) and bridged (cycloheptane) isoxazolidines. We reasoned that a more rigid diol blocking group such as a *trans*-acetonide would favor the *endo* mode of cyclization. Computational studies of INAC of debenzyl D-*lyxo*-hept-6-enose **6** containing a 3,4-*trans*-acetonide show that the *endo*-TS **5a** (leading to a cycloheptane) is about 4.2 kcal mol^{−1} more stable than *exo*-TS **5b** (leading to a cis-fused cyclohexane).¹¹ To our delight, treatment of **6**, readily available from D-ribose (vide infra), with *N*-methylhydroxylamine in acetonitrile indeed afforded exclusively bridged bicyclo[4.2.1]isoxazolidine **7** in excellent yield (Table 1). The INAC should proceed through a chairlike TS with the 3,4-*trans*-diequatorial acetonide. We believed that efficient overlap of bonding orbitals could only be feasible with cycloheptane-*endo*-TS **5a** that experiences less torsional

Table 1. *endo*-Selective INAC Reactions of Hept-6-enoses

entry ^a	aldehyde ^d	cycloadduct	yield ^e
1 ^b			97%
2 ^b			85%
			8%
3 ^c			56%
			29%
4 ^c			93%

^a For experimental details and X-ray crystallographic structures, see the Supporting Information. ^b With *N*-methylhydroxylamine. ^c With *N*-benzylhydroxylamine. ^d Not characterized. ^e Overall isolated yield from the corresponding diol or alcohol.

strain than cyclohexane-*exo*-TS **5b**, leading to exclusive formation of **7**. Furthermore, INAC of D-*xylo*-**8**, L-*gluco*-



11, and D-*ido*-**14** hept-6-enoses all gave cycloheptanes exclusively in excellent yields (Table 1). The stereochemistry of the only or major heterocycle appears to be controlled by the OR group at C-2. The new C–N bond is anti to the axial OR-2 (entry 1) and syn to the equatorial OR-2 (entries 2–4).

With [4.2.1]isoxazolidines readily in hand, transformation into the target molecules is straightforward (Scheme 3). For example, deacetonation of **7** gave diol **16** that underwent regioselective oxidation to give ketone **17**. Hydrogenolysis of the N–O bond and the benzylic C–O bond in **17** produced a calystegine B analogue **18**. Debenzoylation of **12** or **15** followed by oxidation afforded ketone **19** that yielded (*S*)-3-hydroxycalystegine B₅ **20** upon deprotection. Toward tropane synthesis, cycloadduct **13** was debenzoylated and then mesylated to give mesylate **21**. Sequential acid

(4) Gravier-Pelletier, C.; Maton, W.; Dintinger, T.; Tellier, C.; Merrer, Y. L. *Tetrahedron* **2003**, *59*, 8705–8720.

(5) For recent syntheses, see: (a) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465–472. (b) Mans, D. M.; Pearson, W. H. *Org. Lett.* **2004**, *6*, 3305–3308.

(6) For recent syntheses, see: (a) Skaanderup, P. R.; Madsen, R. *J. Org. Chem.* **2003**, *68*, 2115–2122. (b) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705–3717.

(7) (a) Dräger, B. *Nat. Prod. Rep.* **2004**, *21*, 211–223. (b) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471–484.

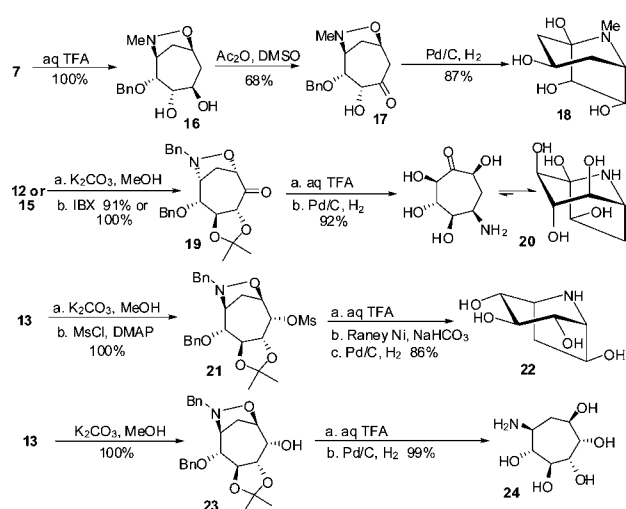
(8) Lounasmaa, M.; Tamminen, T. *Alkaloids* **1993**, *44*, 1–79.

(9) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. *J. Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680.

(10) Shing, T. K. M.; Wong, A. W. F.; Ikeno, T.; Yamada, T. *J. Org. Chem.* **2006**, *71*, 3253–3263.

(11) For details, please refer to the Supporting Information.

Scheme 3. Transformation of Cycloadducts **7**, **12** or **15**, and **13**

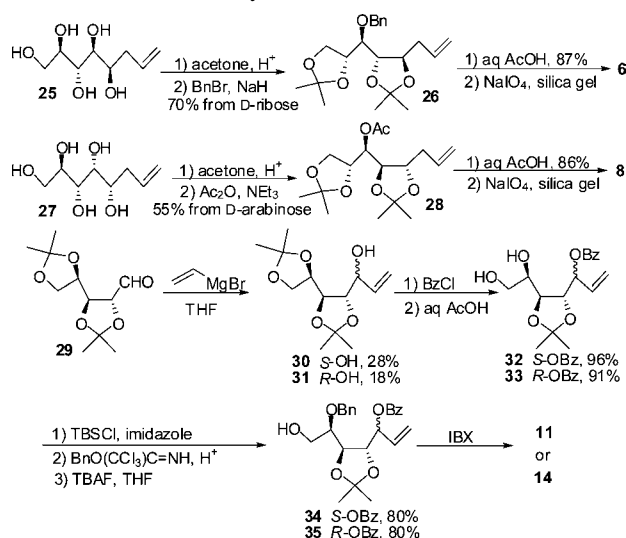


hydrolysis, N–O bond cleavage with concomitant nucleophilic displacement, and debenzoylation of **21** produced tropane **22**. Synthesis of a hydroxylated aminocycloheptane is also shown in Scheme 3 in which **13** was debenzoylated to alcohol **23** that was hydrolyzed and then hydrogenolyzed to give **24**.

Preparation of INAC precursors is shown in Scheme 4. Indium mediated aqueous allylation¹² of D-ribose and D-arabinose gave alkenes **25** and **27** which were readily converted into aldehydes **6** and **8**, respectively. Acetonation of D-xylose afforded aldehyde **29**,¹³ which immediately underwent vinylation to give epimeric alcohols **30** and **31** in 28% and 18% respective overall yields. Both alcohols **30** and **31** were transformed readily into aldehydes **11** or **14**, respectively.

In conclusion, high-yielding and exclusive *endo*-INAC reactions of hept-6-enoses controlled by a *trans*-acetonide

Scheme 4. Syntheses of INAC Precursors



to give bridged bicyclo[4.2.1]isoxazolidines are realized for the first time. This opens a facile synthetic avenue to optically active calystegines, tropanes, and hydroxylated aminocycloheptanes for biological evaluation.

Acknowledgment. This work was partially supported by a CERG from Research Grants Council of HKSAR, China (project no. 402805), and was also partially supported by a Grant-in-Aid for the 21st century COE program “KEIO LCC” from the Ministry of Education, Culture, Sports, Science and Technology, Japan. The authors thank the Research Center for Computational Science, Okazaki National Institute, for their support of the DFT calculations.

Supporting Information Available: Additional information, experimental procedures, and product characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL062621O

(12) Prenner, R. H.; Schmid, B. W. *Leibigs Ann. Chem.* **1994**, 73–78.
(13) Calinaud, P.; Gelas, J. In *Preparative Carbohydrate Chemistry*; Hanessian, S., Ed.; Marcel Dekker, New York, 1997; pp 3–33.