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

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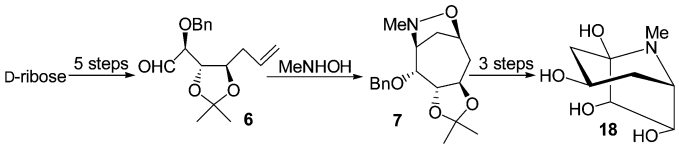
ABSTRACT



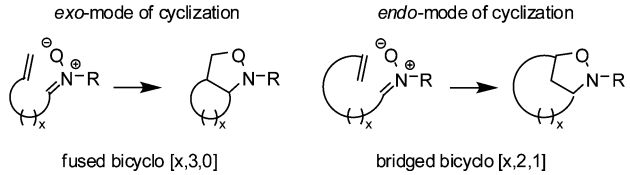
High-yielding *endo*-selective intramolecular nitrone–alkene cycloaddition (INAC) reactions of hept-6-enoses controlled by a *trans*-acetonide to give bridged bicyclo[4.2.1]isoxazolidines exclusively are realized for the first time. The cycloadducts were readily transformed into calystegine, tropane,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

Intramolecular nitrone−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 examples[3] of the formation of a bridged bicyclo[4.2.1] system, i.e., a cycloheptane skeleton from branched sugars, but many examples[1] of unbranched hept-6-enose derivatives give a fused bicyclo[4.3.0] system, i.e., a cyclohexane skeleton. However, the regio- and diastereoselectivity 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



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(2) Tufariello, J. J. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 2, pp 83−168.
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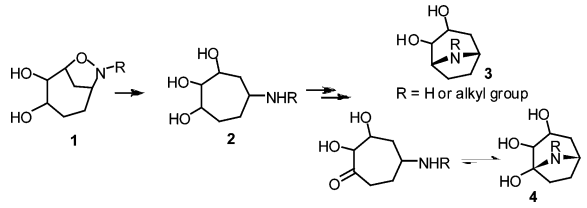
2, proven to be a new class of glycosidase inhibitor.[4] Synthetic manipulation of **2** could lead to alkaloid tropane **3**[5] and calystegine **4**[6] that exhibits specific glycosidase inhibition[7] (Scheme 2). Optically active tropanes are still in

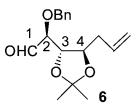
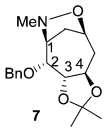
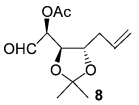
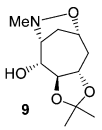
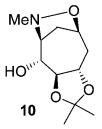
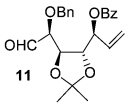
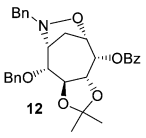
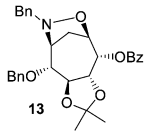
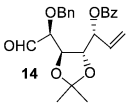
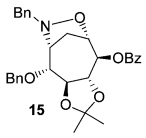
Scheme 2. Catalytic Hydrogenolysis of the N−O Bond in Isoxazolidine **1** and Subsequent Transformation



demand for neuroscience research[8] 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**.

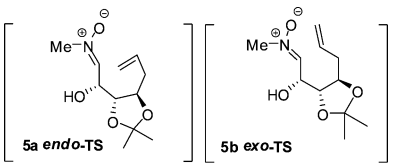
Recently, we reported[10] that *exo*-INAC cyclization was the preferred pathway for hept-6-enoses containing a *cis*-acetonide to give fused isoxazolidine exclusively whereas hept-6-enoses with a 2,3-*O*-*trans*-diacetal gave a mixture of fused (cyclohexane) and bridged (cycloheptane) isoxazolidines. 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 charaterized. [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 B_5 **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.

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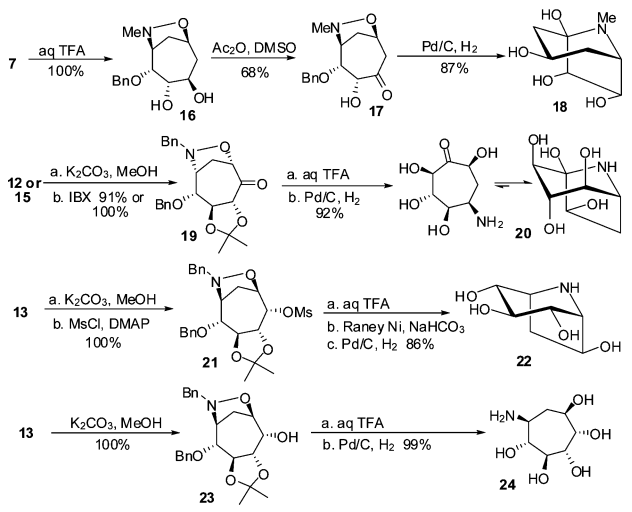
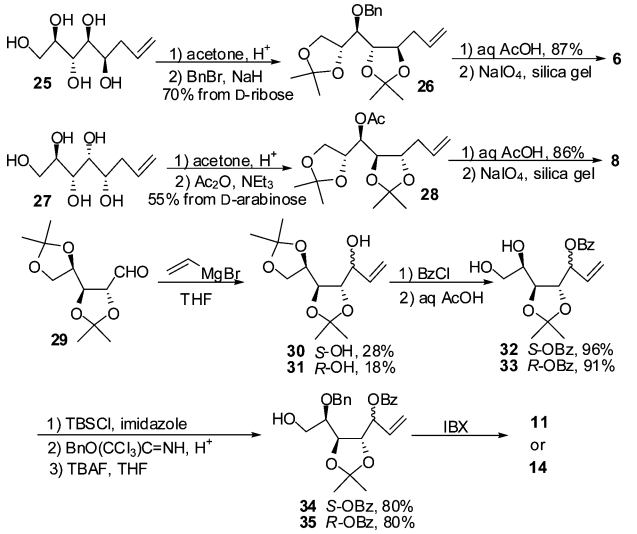
(11) For details, please refer to the Supporting Information.

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



Scheme 4. Syntheses of INAC Precursors



hydrolysis, N−O bond cleavage with concomitant nucleophilic displacement, and debenzylation 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 allylation[12] 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 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.

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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.

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