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Tetrahedron Letters 45 (2004) 5811–5814
Tetrahedron Letters

[3+2] Cycloaddition reactions: a simple entry to the 1-aza-2-oxo-3,4,5,6-tetrahydroxybicyclo[3.3.0]octane ring system

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Received 26 April 2004; revised 28 May 2004; accepted 3 June 2004

Abstract—The [3+2] intramolecular nitrone cycloaddition (INC) reaction on appropriately designed olefinic nitrones derived from D-glucose, having the nitrone at C-1 and α,β-unsaturated ester functionalities at C-5 of the sugar backbone, afforded the isoxazolidine fused carbocycles **11**–**13**, which were subsequently transformed into the chiral, tetrahydroxylated *cis*-azabicyclo[3.3.0]octanones **14**–**18** in good yields.

1. Introduction

Bicyclic lactams with the azabicyclo[3.3.0]octanone ring system are reported to possess serine protease inhibitory activity,[1] and many of them are used as anxiolytics as well to improve brain function.[2] A bicyclic *cis*-lactam having the (1*S*,5*S*)-2-azabicyclo[3.3.0]octane moiety[3] is the basic structural element of the angiotensin converting enzyme (ACE) inhibitor HOE 498. Furthermore, hydrolytic ring opening of the *cis*-lactam of skeleton **1** could furnish novel restricted analogues[4] of GABA, which is regarded as a major inhibitory neurotransmitter. There are many reports on the synthesis of these compounds involving, among others, (i) cyclization of *trans*-2-aminocyclopentane acetic acid with Mukaiyama's reagent under high dilution conditions,[5] (ii) tandem [4+2]/[3+2] cycloaddition of a nitroalkene to an alkene followed by hydrogenolysis of the resulting cycloadduct,[6] (iii) iodolactamization of an olefinic amide through an *N*,*O*-bis(trimethylsilyl)imidate derivative,[7] (iv) addition of the ketene acetal or titanium enolate of a 2-pyridylthioester to an acyliminium ion followed by ring closure,[8] and (v) radical cyclization of an *N*-(1-cycloalken-1-yl)-α-haloacetamide.[9] Introduction of chirality has been achieved by using chiral amino acids, by chiral induction or by kinetic resolution of racemic mixtures. However, most of these methods involve long procedures and the use of costly reagents so that the development of expedient and flexible synthetic routes to novel classes of enantiomerically pure bicyclic lactams continues unabated. Literature reports as well as our experience with the application of intramolecular nitrone cycloaddition (INC) reactions[10,11] on various D-glucose derived substrates allowed us to envisage that an appropriate α,β-unsaturated ester generated from a C-5 aldehyde should undergo prompt cycloaddition with a nitrone at C-1 (formed by reaction of the latent aldehyde with *N*-benzyl hydroxylamine). The reaction is expected to be driven by the favourable interaction of the HOMO of the nitrone component with the LUMO of the *Z*-substituted olefin, leading to an isoxazolidine product **2**. Subsequent hydrogenolytic opening of the isoxazolidine ring should be accompanied by spontaneous lactamization, offering an expedient route to chiral *cis*-fused bicyclic lactams **1**. Figure 1 summarizes retrosynthetically our approach.

2. Results and discussion

5-Aldo-1,2-*O*-cyclohexylidene-α-D-glucofuranose (**5**) and 5-aldo-1,2-*O*-isopropylidene-α-D-glucofuranose (**6**) were prepared from the respective dicyclohexylidene-/diacetone-D-glucose derivatives **3** and **4** through benzylation ($PhCH_2Br$, CH_2Cl_2, 50% aq NaOH, n-$Bu_4N^+Br^-$, rt, 12 h) of the C-3–OH followed by selective deprotection of the 5,6-ketal with 80% HOAc and vicinal diol

Keywords: Nitrone cycloaddition reaction; Synthesis; Bicyclic lactams; Azabicyclo[3.3.0]octane; D-glucose.
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doi:10.1016/j.tetlet.2004.06.017

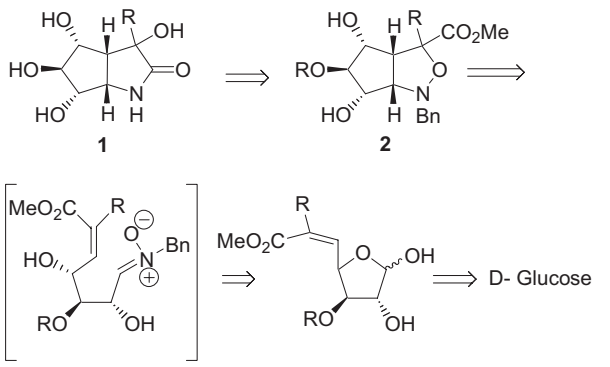


Figure 1. Retrosynthetic analysis for the azabicyclo[3.3.0]octanone ring system.

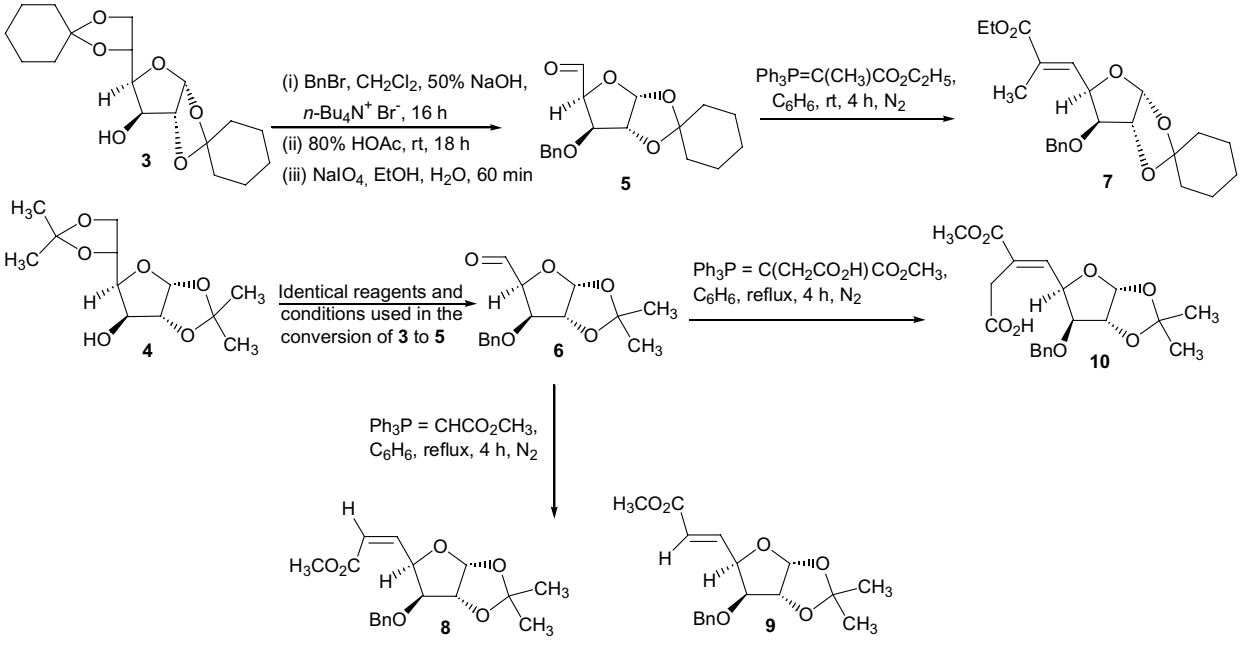
cleavage using $NaIO_4$ in aq EtOH. The conjugated esters used in this study were prepared by Wittig reactions. Thus, treatment of **5** with 2-(triphenylphosphanylidene)propionic acid ethyl ester led to the α,β-unsaturated ester **7**[12] (65%). In a similar manner, the aldehyde **6** afforded **10** (71%) with 2-(triphenylphosphanylidene)succinic acid 1-methyl ester.[13] However, a mixture of olefinic compounds **8** (42%) and **9** (21%) resulted when triphenylphosphanylidene acetic acid methyl ester was reacted with **6** (Scheme 1).

Removal of protection from the 1,2 positions of **7**, **8** and **10** created latent aldehydes at C-1, which were reacted with *N*-benzyl hydroxylamine (followed by diazomethane treatment in the case of **10**) to generate the corresponding isoxazolidine derivatives **11**–**13** in good yields, conceivably through spontaneous cyclization (the INC reaction)[14] of the expected nonisolable nitrones. Subsequent reductive opening[15] of the isoxazolidine rings in **11** and **12** under hydrogenolytic conditions[16] directly furnished the respective chiral bicyclic lactams **14** and **15**. Similar reaction with **13** afforded the expected lactam **17**. Acetylation of **15** and **17** furnished their tetra- and tri-acetate derivatives **16** and **18**, respectively, whose well-resolved ^1H NMR spectra proved very helpful in structure elucidation (Scheme 2).

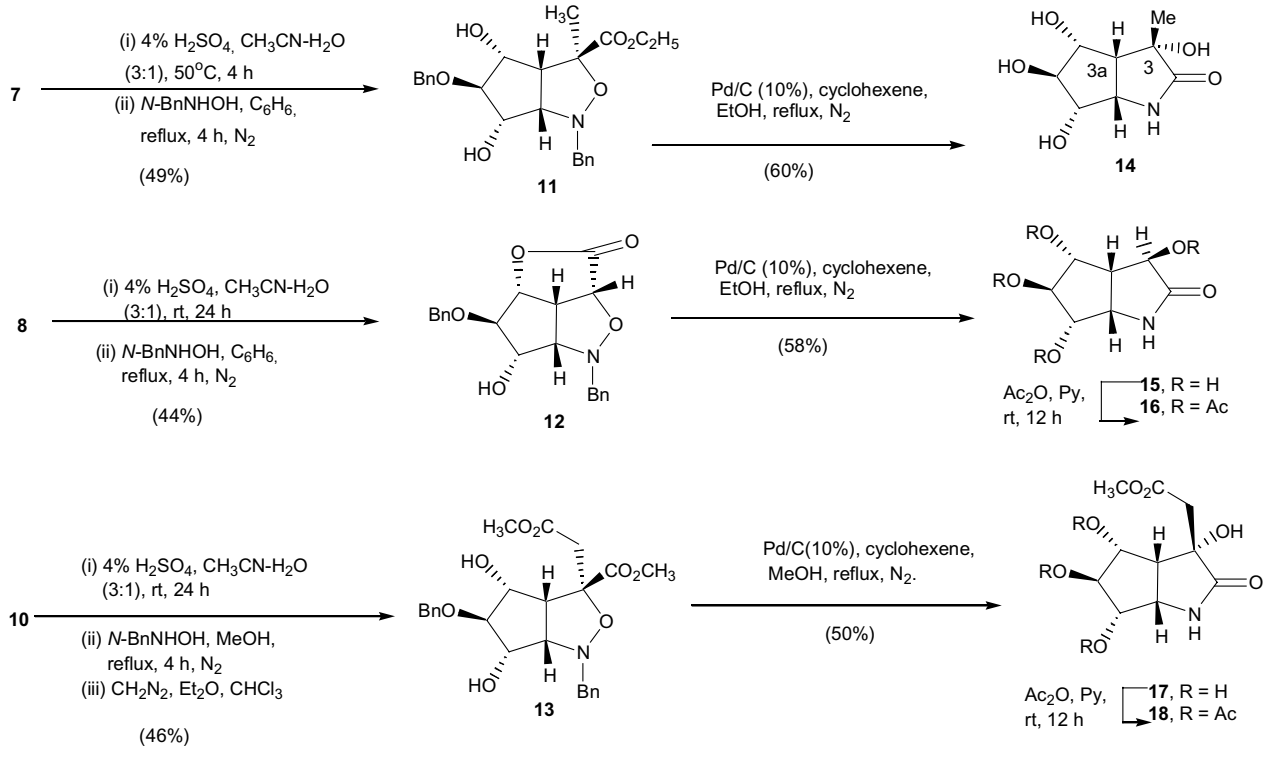
The structures of the products were deduced unequivocally from spectral studies. Of particular importance was the finding that in the ^1H NMR of **9**, the β-hydrogen atom has a more downfield chemical shift (δ 6.94 vs 6.40) and the H–C=C–H coupling constant is larger (15.7 vs 11.7) when compared to those of **8**, which settled the orientation of the double bond in these compounds. The δ values for the β-hydrogens in **7** and **10** (6.89 and 7.06, respectively) are close to that of the corresponding proton in **9**, suggesting the geometry shown.

The formation of the isoxazolidine rings in **11**–**13** was concluded from their ^1H and ^{13}C NMR spectra. The IR spectrum of **12** indicated the formation of a five-membered lactone ring (ν_{max} at 1775 cm^{-1}), proving that the hydroxyl (generated at C-4) and the carbomethoxy groups must be on the same face of the intermediate hydroxy ester. The stereochemistry at C-2, C-3 and C-4 (glucose numbering) in **12** should be the same as the corresponding carbons in D-glucose, as these were not disturbed during the reaction sequence. As the two olefinic protons in **8** were *cis*, they should also be *cis* related in product **12**.

The *cis* ring juncture shown is energetically favoured in the case of the bicyclo[3.3.0]octane[17] system. Molecular modelling studies (Chem. Office 6.0 using the MM2 programme followed by molecular dynamics) revealed that the minimum energy conformer of the *cis* isomer **14** has far less steric energy (12.9 kcal/mol) than its *trans* isomer (26.4 kcal/mol). Similarly, the structures and stereochemistries of **10** and **13** were concluded from the



Scheme 1. Preparation of olefin-esters **7**–**10**.



Scheme 2. Conversion of INC reaction products to bicyclic lactams.

stereochemistry of the olefin as well as from the absence of a lactone moiety in the compounds, showing that the C-4 OH and C-3 CO_2CH_3 groups are not close in space.

For the lactam **14**, the cross peaks between C-3a H and C-3 CH_3 in its NOESY spectrum indicated their *cis* relationship; the absence of similar peaks between C-3 H and C-3a H in the NOESY spectrum of **15** suggested their *trans* disposition. Likewise, the structure of **17** was deduced based on its formation from **13**.

3. Conclusion

In summary, we have developed a strategy to synthesize chiral bicyclic lactam rings using intramolecular 1,3-dipolar nitrone cycloaddition reactions on D-glucose derived substrates. The simplicity and versatility of precursor preparation, the feasibility of carrying out the precursor assembly and the cycloaddition in a tandem process, and the efficacy of the reaction make the present approach one of the simplest and most practical to such substituted azabicyclo[3.3.0]octanones. The scope and limitation of the method for the synthesis of other systems with different ring sizes is under study.

Acknowledgements

The work has been supported by a grant from the Department of Science and Technology (Govt. of India). One of the authors (A.R.) gratefully acknowledges the Council of Scientific and Industrial Research for providing a Junior Research Fellowship.

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12. Typical procedure for α,β-unsaturated ester **7**. 2-(Triphenylphosphanylidene)propionic acid ethyl ester (2.87 g, 7.9 mmol) was added to a benzene solution of the aldehyde **5** (1.70 g, 5.3 mmol) and the mixture was stirred at rt under N_2 for 4 h. The solvent was evaporated in vacuo, and the crude product was purified by chromatography over silica gel eluting with $CHCl_3$–Pet.ether (2:3) to afford **7** as a colourless thick oil; $[\alpha]_D^{25}$ −36.8 (*c* 0.38, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.31 (t, 3H, $J = 7.1$ Hz), 1.40–1.74 (m, 10H), 1.81 (s, 3H), 3.95 (d, 1H, $J = 3.1$ Hz), 4.24 (dq, 2H, $J = 0.6$, 7.0 Hz), 4.47 (d, 1H, $J = 12.0$ Hz), 4.64 (d, 1H, $J = 12.0$ Hz), 4.65 (d, 1H, $J = 3.8$ Hz), 4.92 (dd, 1H, $J = 3.0$, 7.7 Hz), 6.00 (d, 1H, $J = 3.7$ Hz), 6.89 (dd, 1H, $J = 1.4$, 7.7 Hz), 7.29 (m, 5H); ESI$^+$, *m/z*: 425 (M^++Na).
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14. Typical procedure for INC reaction on **7**. Compound **7** (1.40 g, 3.5 mmol) was dissolved in 4% H_2SO_4 in CH_3CN–H_2O (3:1) mixture (20 mL) and kept at 50 °C for 4 h when TLC showed complete disappearance of the starting material. The solution was cooled to rt, neutralized with solid $CaCO_3$, filtered, and the solvent was evaporated under reduced pressure to afford a crude residue (1.0 g), which was dried over P_2O_5 in vacuo. To the benzene solution (50 mL) of the above crude residue was added *N*-benzyl hydroxylamine (430 mg, 3.5 mmol) and the solution was heated at reflux under N_2 for 4 h. The crude obtained after evaporation of the solvent was purified by chromatography on a silica gel column using $CHCl_3$–MeOH (99.5:0.5) as eluent to afford **11** (725 mg) as a foamy material; [Found: C, 67.45; H, 6.76; N, 3.23. $C_{24}H_{29}NO_6$ requires C, 67.43; H, 6.84; N, 3.28]; $[\alpha]_D^{25}$ −65.4 (*c* 0.58, $CHCl_3$); IR (KBr): ν_{max} 3435, 1725, 1453, 1371, 1024, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.27 (t, 3H, $J = 7.1$ Hz), 1.50 (s, 3H), 1.83 (br s, 1H, exchangeable), 2.35 (br s, 1H, exchangeable), 3.45 (m, 2H), 3.63 (t, 1H, $J = 8.4$ Hz), 3.86–3.94 (2H signal, one d merged at 3.88, $J = 13.3$ Hz), 4.04 (t, 1H, $J = 8.1$ Hz), 4.21 (q, 2H, $J = 7.1$ Hz), 4.26 (d, 1H, $J = 13.3$ Hz), 4.72 (d, 1H, $J = 12.0$ Hz), 4.78 (d, 1H, $J = 12.0$ Hz), 7.34 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 18.5, 54.9, 60.1, 62.0, 71.9, 73.4, 73.5, 75.9, 84.2, 89.5, 128.0, 128.2 (2C), 128.3, 128.8 (2C), 128.9 (2C), 129.3 (2C), 137.1, 138.9, 174.8; FABMS, *m/z*: 428 (M^++1).
15. Typical procedure for the reductive cleavage of the isoxazolidine ring and removal of the benzyl group from **11**. A mixture of **11** (300 mg, 0.7 mmol), (10%) Pd/C (150 mg), cyclohexene (1.5 mL) and dry EtOH (25 mL) was heated at reflux under N_2 for 4 h. The catalyst was filtered off, the solvent was evaporated and the crude product was purified by reverse phase chromatography (adsorbent: LiChroprep® RP-18, particle size: 25–40 μm) using water as eluent to yield **14** as a white solid (85 mg, 60%); mp 158–159 °C; [Found: C, 47.29; H, 6.38; N, 6.83. $C_8H_{13}NO_5$ requires C, 47.29; H, 6.45; N, 6.89]; $[\alpha]_D^{25}$ −2.7 (*c* 0.29, MeOH); IR (KBr): ν_{max} 3374, 1693, 1248, 1495, 1103, 1010, 653 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz): δ 1.32 (s, 3H), 2.56 (t, 1H, $J = 8.8$ Hz), 3.59 (dd, 1H, $J = 4.0$, 8.4 Hz), 3.68 (dd, 1H, $J = 1.9$, 6.2 Hz), 3.71 (dd, 1H, $J = 2.0$, 6.6 Hz), 3.94 (t, 1H, $J = 8.8$ Hz); ^{13}C NMR (D_2O, 75 MHz): δ 25.2, 50.1, 56.9, 72.4, 74.5, 79.0, 81.2, 179.4; FABMS, *m/z*: 204 (M^++1).
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