Pergamon

Tetrahedron Letters 42 (2001) 4755–4757

TETRAHEDRON LETTERS

A concise synthesis of the (−)-allosamizoline aminocyclopentitol based on pyridinium salt photochemistry

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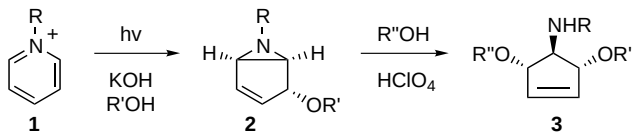
Received 11 April 2001; accepted 20 April 2001

Abstract—The (−)-allosamizoline aminocyclopentitol was prepared by use of a route featuring pyridinium salt photochemical synthesis of the aminocyclopentene core, enzymatic desymmetrization, Wittig rearrangement to introduce the hydroxymethyl side chain, and regiocontrolled epoxide ring opening. © 2001 Published by Elsevier Science Ltd.

The functionalized 3-aminocyclopentene forming photoreaction of pyridinium salts, originally reported in 1983,[1] is unique in its ability to generate stereochemically and functionally complex substances from simple starting materials.[2] This feature is exemplified by the general sequence outlined in Scheme 1, in which irradiation of a pyridinium salt **1** in basic aqueous or alcoholic solution leads to formation of the bicyclic-aziridine **2**.[3] This is followed by stereocontrolled acid-catalyzed aziridine ring opening to produce the aminocyclopentene derivative **3**.

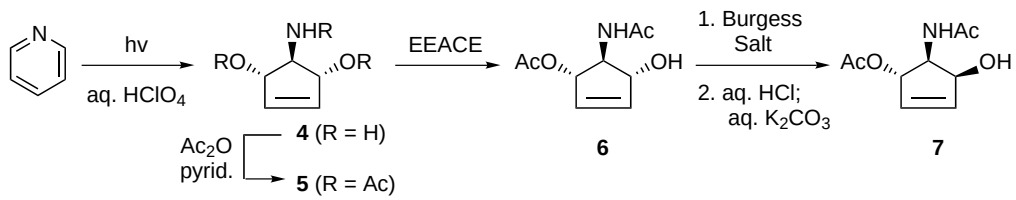


Scheme 1.

In recent efforts aimed at demonstrating the synthetic potential of this chemistry, we have shown that irradiation of pyridine in aqueous perchloric acid leads to direct generation of the *trans*,*trans*-aminocyclopentenediol **4**, isolated as the triacetyl derivative **5**.[2] Desymmetrization of **5** by using the electric eel acetyl cholinesterase provides the mono-alcohol **6** (ca. 80% ee), which can be converted to the *cis*,*trans*-analog **7** by employment of the hydroxyl inversion procedure described by Wipf[4] (Scheme 2).

This chemistry allows rapid access to a variety of functionally and stereochemically diverse, enantiomerically enriched aminocyclopentenes, which can serve as versatile starting materials in routes for the synthesis of biomedically important, natural and non-natural, cyclic (e.g. aminocyclopentitols) and acyclic (e.g. aminoalditols) polyhydroxylated amines. Preliminary studies probing the dexterity of this methodology have, thus far, resulted in a concise synthesis of the potent mannosidase inhibitor (+)-mannostatin-A[5] and several of its previously unknown analogs.[6]

Below, we describe how this methodology can employed as a key element in the design of routes for



Scheme 2.

Keywords: pyidinium salt; photochemistry; aminocyclopentene synthesis; epoxide ring opening.
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0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00858-9

the synthesis of hydroxymethyl branched derivatives of the aminocyclopentitol family of glycosidase inhibitors.[7] The focus of this effort is the aminocyclopentitol **10**, the core structural unit in (–)-allosamizoline, a component of the chitinase inhibitor, allosamidine.[8] The plan for synthesis of **10** (Scheme 3) takes advantage of the functionality present in amidocyclopentenols **8**, prepared by sequences like those shown in Scheme 2, to introduce side chain hydroxymethyl or equivalent functionality in a highly stereo- and regiocontrolled manner. In this approach, Wittig rearrangement of functionalized derivatives of **8** is used to generate 3-hydroxymethyl substituted amidocyclopentenes **9**. Stereocontrolled dihydroxylation of **9** then provides the aminocyclopentitol core of (–)-allosamizoline or its stereoisomeric analogs.

The route developed for synthesis of **10** (Scheme 4) begins with the pyridine derived amidocyclopentenol **11**.[5] Following the procedure developed by Still,[9] **11** is transformed to *cis*,*trans*-hydroxymethylcyclopentene **13**. This sets the stage for introduction of the *trans*-diol functionality present in the target by use of epoxide formation and ring opening. We reasoned that the difficulty encountered in controlling the stereochemistry/regiochemistry of *trans*-dihydroxylation processes in routes to closely related allosamizoline precursors[10] could be avoided by selective introduction of an *N*,*O*-linked acetonide as found in **14**. Analysis of models (Fig. 1) suggests that the *endo* methyl group in **14** would both reinforce homoallylic alcohol[11] control of epoxidation stereochemistry and direct desired regioselective hydroxide promoted nucleophilic opening of the epoxide ring. In the event, **14**, prepared by TBAF promoted desilylation and acetonide formation, undergoes clean stereoselective reaction with MCPBA to form epoxide **15**. In addition, this substance is selectively converted to triol **16**[12a] upon treatment with 0.5N NaOH.

Assignment of the *cis*,*trans*,*cis*,*trans* stereochemistry in **16** is made by use of ^{1}H NMR spectroscopic techniques including COSY and NOE.[13] Significant in this regard are the strong NOEs observed for H_5 and H_2 upon

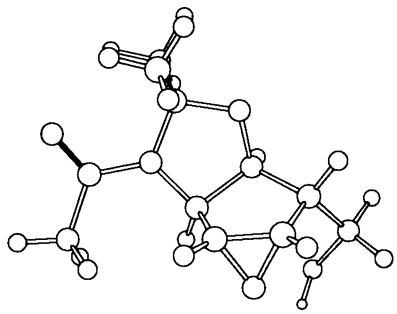
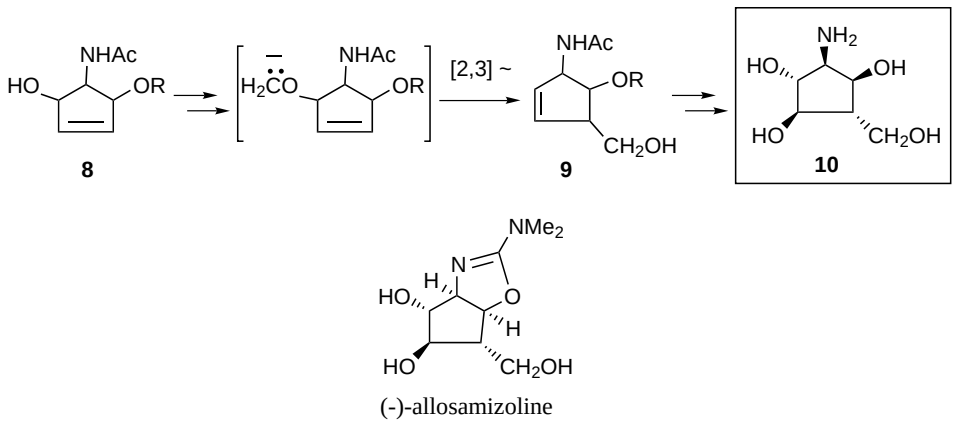
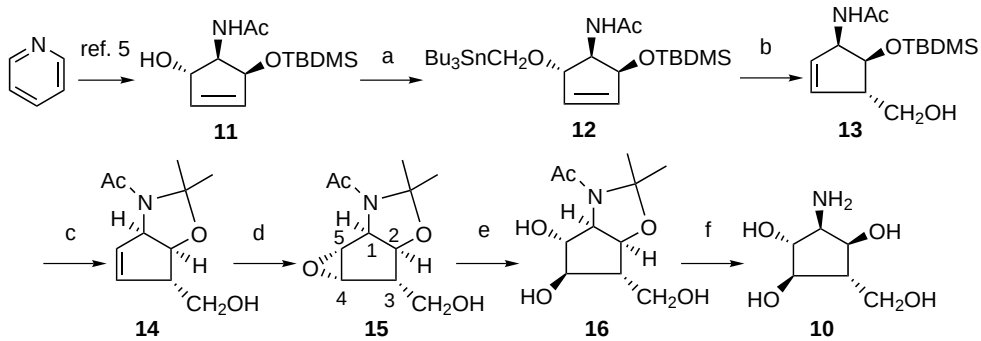


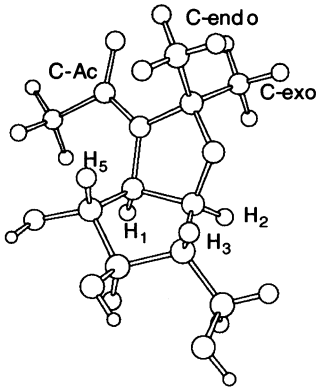
Figure 1. Macromodel globally energy minimized structure of epoxide **15**.



Scheme 3.



Scheme 4. (a) KH, THF, 0°C, ICH_2SnBu, 25°C, 95%; (b) BuLi, THF, –78°C, 50%; (c) TBAF, THF, 25°C, $Me_2C(OMe)_2$, PTSA, toluene, 82%; (d) MCPBA, CH_2Cl_2, 25°C, 84%; (e) 0.5N NaOH, H_2O–THF, 70°C; (f) 4N HCl, 70°C, 91% two steps.



Distances (Angstoms)	
C-endo - H_5	3.50
C-endo - H_3	4.25
C-exo - H_2	3.09
C-exo - H_1	3.93
C-Ac - H_1	2.84
C-Ac - H_5	3.95

Figure 2. Macromodel globally energy minimized structure of amino-polyol **16**.

irradiation of the *endo* and *exo* methyl protons, respectively. In addition, irradiation of the acetyl methyl protons results in a strong NOE for H_1. The effects correlate well with distance measurements derived from a macromodel, globally energy minimized structure of **16** (Fig. 2).

Simultaneous removal of the acetonide and amide groups by treatment of **16** with aq. HCl completes the synthesis of the (−)-allosamizoline aminocyclopentitol **10**.[12b]

Acknowledgements

Financial support for this work from the NIH (GM-27250) is acknowledged. Sung-Ju Cho and Xiaomei Wu are acknowledged for their preliminary studies on this problem.

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12. Spectroscopic data for (a) **16**: ^{1}H NMR (D_2O): 1.69 (s, 3H), 1.85 (s, 3H), 2.23 (m, 1H), 2.42 (s, 3H), 3.84 (dd, J=7.5, 11.4 Hz, 1H), 3.94 (m, 2H), 4.22 (t, J=8.6 Hz, 1H), 4.42 (dd, J=6.1, 8.6 Hz, 1H), 4.62 (dd, J=1.65, 6.1 Hz, 1H). ^{13}C NMR (D_2O): 174.29 (**C**=O), 100.04, 83.91, 80.05, 79.01, 66.52, 63.18, 51.59, 28.98, 26.33, 25.43; (b) to our knowledge, **10** has not been prepared and characterized previously; [α]=+33.14 (*c* 0.1, EtOH). ^{1}H NMR (D_2O): 1.72 (m, 1H), 2.77 (dd, J=6.4, 9.7 Hz, 1H), 3.51–3.42 (m, 2H), 3.59 (dd, J=4.8, 11.5 Hz, 1H), 3.65 (dd, J=8.1, 9.7 Hz, 1H), 3.78 (dd, J=3.6, 6.4 Hz, 1H). ^{13}C NMR (D_2O): 79.7, 74.55, 69.26, 60.47, 56.01, 52.75.
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