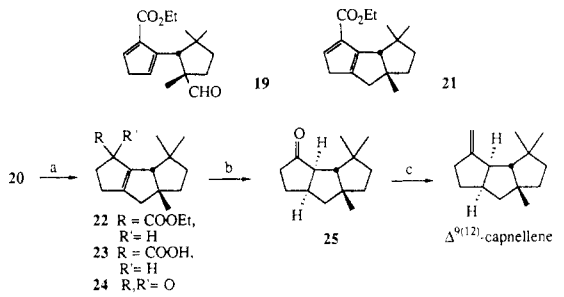

(a) (1) Mg, MeOH, rt, 64%; (2) 10% NaOH, 60 °C, 100%; (3) LDA, -78 °C, THF, HMPA; (4) O_2, rt; H_3O^+; (5) $Pb(OAc)_4$, 57%, three steps overall; (b) (1) Li, NH_3; (2) PDC, CH_2Cl_2, 62% overall; (c) $CH_2{=}PPh_3$

Acid **23**, formed by hydrolysis of **22**, was treated with LDA followed by oxygen to give a hydroxy acid, which was cleaved by lead tetraacetate to form the unsaturated ketone **24**. The ketone was then reduced with lithium in ammonia, and the product was oxidized with PDC in methylene chloride to give saturated ketone **25**. This has spectra identical with those of the ketone obtained earlier by Little and co-workers.[14] The reaction of **25** with a Wittig reagent to give $\Delta^{9(12)}$-capnellene has been reported.[14]

In summary, the ester-substituted fulvenes formed from the condensation of cyclopentadienecarboxylates can be use to construct linearly fused tricyclopentanoids by intermolecular[15] or intramolecular reactions with the double bonds of enamines or enols.

Acknowledgment. We are grateful to the National Institutes of Health for financial support of this research. We thank Professor T. Hudlicky for helpful suggestions and Professor R. D. Little for providing the spectra of compound **25**.

Supplementary Material Available: Schemes for the preparation of the reaction intermediates and NMR spectra of the compounds reported in this paper (37 pages). Ordering information is given on any current masthead page.

(14) Little, R. D.; Carroll, G. L. *Tetrahedron Lett.* **1981**, *22*, 4389. Little, R. D.; Carroll, G. L.; Petersen, J. L. *J. Am. Chem. Soc.* **1983**, *105*, 928.

(15) see also Wu, T.-C.; Houk, K. N. *J. Am. Chem. Soc.* **1983**, *105*, 5308.

Stereoselective Synthesis of 3-Amino 1,2-Diols via Intermolecular Pinacol Cross-Coupling of α-[(Alkoxycarbonyl)amino] Aldehydes with Aliphatic Aldehydes. Short Asymmetric Syntheses of Two 2,3,6-Trideoxy-3-amino Sugars

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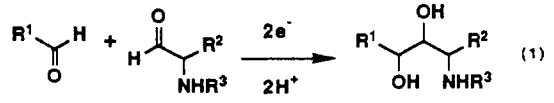
Received April 30, 1990

Summary: *syn,syn*-3-Amino 1,2-diols are prepared via a pinacol cross coupling reaction between *N*-Cbz- or *N*-Boc-α-amino aldehydes and aliphatic aldehydes. Application of this methodology to the syntheses of two amino sugars starting from *N*-Cbz-L-aspartic acid are described.

Amino sugars containing the 3-amino 1,2-diol subunit are important constituents of a variety of antibiotics.[1] Consequently, there has been a long-standing interest in the synthesis of such compounds. The majority of synthetic efforts in this area have focused on manipulation of naturally occurring carbohydrates.[1] However, in the last decade numerous acyclic synthetic approaches to these sugars have appeared.[2] One potentially versatile synthesis of the 3-amino 1,2-diol unit would involve the reductive coupling of an α-amino aldehyde with another aldehyde (an intermolecular pinacol cross-coupling reaction) (eq 1).



(1)

Noteworthy features of this reaction would be the construction of the diol group in a single carbon–carbon bond forming reaction starting from readily available and optically active starting materials. We have recently reported the first efficient and stereoselective method for coupling two different, yet electronically similar aldehydes, employing the easily prepared vanadium(II) reagent, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**).[3] Successful pinacol cross-coupling generally requires slow addition of a chelating aldehyde to a mixture of **1** and a nonchelating aldehyde, followed by an aqueous workup. α-[(Alkoxycarbonyl)amino] aldehydes[2c] seemed likely candidates for this reaction. Herein, we report a new route to 3-amino 1,2-diols employing such aldehydes and apply this method to the syntheses of two amino sugars starting from *N*-Cbz-L-aspartic acid.

Slow addition (ca. 1 h) of *N*-Cbz- or *N*-Boc-α-amino aldehydes to a mixture of **1** and an aliphatic aldehyde in dichloromethane leads to the stereoselective and high yield synthesis of *N*-Cbz- or *N*-Boc-*syn,syn*-3-amino 1,2-diols (Table I).[4] The major isomer (*syn,syn*) is that expected from chelation control.[5,6] The α-[(alkoxycarbonyl)amino]

(1) (a) Reden, J.; Durckheimer, W. *Top. Curr. Chem.* **1979**, *83*, 105. (b) Umezawa, S. *Pure Appl. Chem.* **1978**, *50*, 1453. (c) Horton, D.; Wander, J. D. In *Carbohydrates: Chemistry and Biochemistry*; Pigman, W. W., Horton, D., Eds.; Academic: New York, 1980; Vol. 1B, pp 643-760.

(2) For reviews that contain discussions concerning the acyclic synthesis of amino sugars, see: (a) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (b) Hauser, F. M.; Ellenberger, S. R. *Chem. Rev.* **1986**, *86*, 35. (c) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.

(3) Freudenberger, J. H.; Konradi, A. W.; Pedersen, S. F. *J. Am. Chem. Soc.* **1989**, *111*, 8014.

(4) Determining the ratio of diastereomers obtained from these reactions by ^1H and ^{13}C NMR spectroscopy is complicated by the presence of rotamers resulting from the (alkoxycarbonyl)amino group. See the supplementary material for further details. The *syn,syn* stereochemistry was established via an X-ray structural analysis of the hydroxyoxazolidinone obtained from reacting **2** with 1 equiv of sodium hydride in tetrahydrofuran.

(5) For reviews of chelation-controlled addition reactions, see: (a) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer Verlag: Berlin, 1986. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556. See ref 2c for specific examples of chelation-controlled reactions of *N*-protected α-amino aldehydes.

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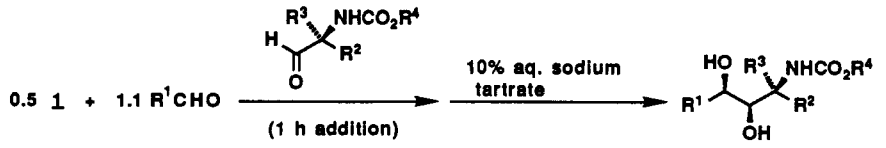
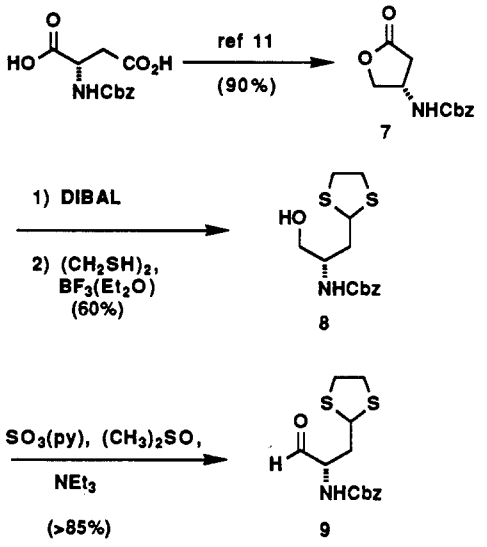
Table I. Synthesis of 3-[*N*-(Alkoxycarbonyl)amino] 1,2-Diols[a]



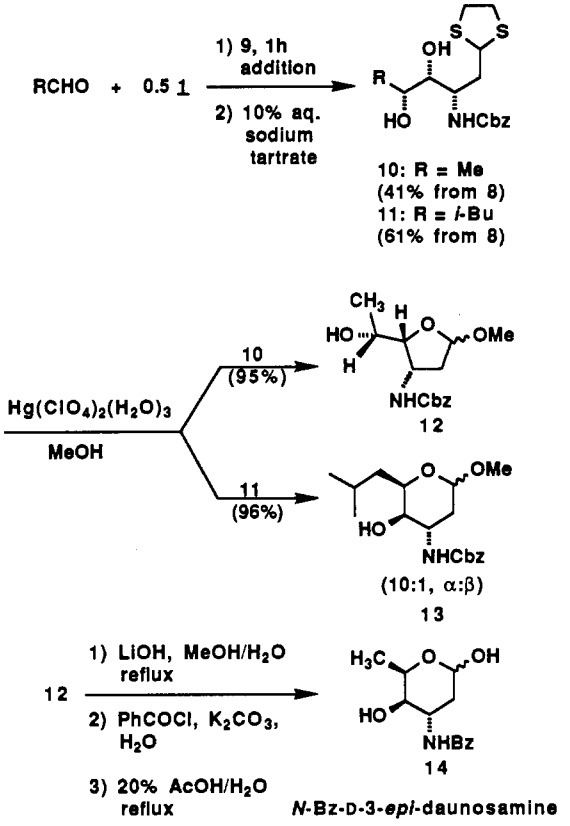
entry	R^1	R^2	R^3	R^4	yield, %	compd no.
1	$PhCH_2CH_2$	$PhCH_2$	H	*t*-Bu	67[b]	2
2	*i*-Pr	*i*-Pr	H	*t*-Bu	70[b]	3
3	*i*-Bu	$-(CH_2)_3NH-$	H	$PhCH_2$	92[c,d]	4
4	*n*-C_7H_{15}	CH_3	CH_3	$PhCH_2$	88[e,f]	5

[a] See supplementary material for a general experimental procedure employing in situ generated 1. [b] One major diol was obtained (ds >20:1). [c] A 5:1 mixture of diols was obtained. [d] The product is derived from (*S*)-prolinal. [e] One major diol was obtained (ds >50:1). [f] The product is a racemic mixture.

Scheme I



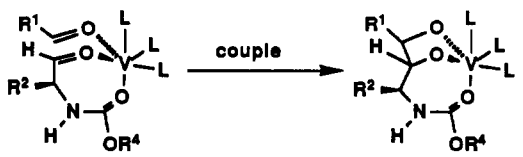
Scheme II



aldehydes used in the coupling reactions were derived from Swern oxidation of the corresponding 2-[(alkoxycarbonyl)amino] alcohols and used without further purification.[7] No epimerization of the α-amino aldehydes was observed during the course of the reactions.[8]

With an efficient construction of *syn,syn*-3-amino 1,2-diols in hand, we set out to develop a synthesis of the amino sugar D-3-*epi*-daunosamine (6).[2b,9] D-3-*epi*-Daunosamine is one diastereomer of a class of 2,3,6-trideoxy-3-amino hexoses that are important constituents of the anticancer antibiotics daunomycin and adriamycin.[10] Our strategy is outlined in Schemes I and II and begins with commercially available *N*-Cbz-L-aspartic acid. The lactone (7) was prepared in two steps by literature methods in 90% yield and on large scales (>50 g).[11] Reduction of 7 was accomplished with DIBAL (1.0 equiv, CH_2Cl_2, −78 °C) to afford an intermediate lactol, which was used without purification and opened (1,2-ethanedithiol, $BF_3(Et_2O)$, CH_2Cl_2) to give the hydroxydithiolane (8) in 60% yield from 7. Oxidation of 8 with sulfur trioxide pyridine complex in dimethyl sulfoxide with triethylamine present[12] provided the *N*-Cbz-α-amino aldehyde (9) (Scheme I),

(6) The term "chelation-controlled" is used to identify a predictive model for the stereochemical outcome of these reactions (illustrated below). This model is not meant to suggest what the reactive intermediates are in this reaction.



(7) Luly, J. R.; Dellaria, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(8) Analysis was performed on the Mosher esters of the hydroxyoxazolidinones prepared by treatment of the 3-[*N*-(alkoxycarbonyl)amino] 1,2-diols with 1 equiv of sodium hydride in tetrahydrofuran. See the supplementary material for further details.

(9) For a review of syntheses of this sugar and its diastereomers through 1986, see ref 2b. For syntheses after 1986, see: (a) Herczegh, P.; Zsely, M.; Kovacs, I.; Gyula, B.; Sztaricskai, F. J. *Tetrahedron Lett.* **1990**, *31*, 1195. (b) Midland, M. M.; McLoughlin, J. I. *Ibid.* **1988**, *29*, 4653. (c) Dai, L.; Lou, B.; Zhang, Y. *J. Am. Chem. Soc.* **1988**, *110*, 5195.

(10) (a) Remers, W. R. *The Chemistry of Antitumor Antibiotics*; Wiley Interscience: New York, 1979; Vol. 1, Chapter 2. (b) Henry, D. W. *Cancer Treat Rep.* **1979**, *63*, 845. (c) Brown, J. R. *Prog. Med. Chem.* **1978**, *15*, 125. (d) Arcamone, F. In *Topics in Antibiotic Chemistry*; Sammes, P. G., Ed.; John Wiley and Sons: New York, 1978; Vol. 2, pp 99–239.

(11) (a) McGarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T. *J. Am. Chem. Soc.* **1986**, *108*, 4943. (b) Lutz, W. B.; Ressler, C.; Nettleton, D. E.; du Vineaud, V. *Ibid.* **1959**, *81*, 167.

(12) Hamada, Y.; Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 1921.

which was used in the subsequent coupling reactions without purification.

Slow addition of **9** (1 equiv over 45 min) to a dichloromethane solution of acetaldehyde (2 equiv) and **1** (0.75 equiv) at 0 °C, followed by workup with 10% (w/v) aqueous sodium tartrate, gave an 8:2:1 mixture of three diastereomers from which the major cross-coupled product (**10**) was isolated by flash chromatography in 41% yield from **8** (Scheme II). An excess of acetaldehyde and **1** has been found to be optimum. Addition of **9** (1 equiv over 45 min) to a solution of **1** (0.5 equiv) and isovaleraldehyde (1.1 equiv) at 25 °C gave a single product (**11**), obtained in 61% yield from **8** (Scheme II). The poor stereoselectivity observed in the acetaldehyde cross-coupling reaction is presumably a consequence of the low steric requirements of the acetaldehyde methyl group.

The dithiolane protecting group in **10** was removed using $Hg(ClO_4)_2(H_2O)_3$[13] in methanol to give a mixture of methyl *N*-Cbz-D-furanosides (**12**) (2:1 at the anomeric carbon) in 95% yield.[14] The overall yield of **12** from *N*-Cbz-L-aspartic acid was 21%. To confirm its relative stereochemistry, compound **12** was transformed into the known *N*-benzoyl-D-3-*epi*-daunosamine (mp 218–220 °C; lit.[9c,15] mp 215–218 °C) in 60% yield (Scheme II). Reaction of **11** with $Hg(ClO_4)_2(H_2O)_3$ in methanol gave methyl *N*-Cbz-D-pyranoside (**13**) in 96% yield (Scheme II).[14,16] The overall yield of **13** from *N*-Cbz-L-aspartic acid was 31%.

The syntheses described above represent a new and stereoselective approach for construction of the 3-amino 1,2-diol unit. The tolerance of **1** toward relatively acidic and reactive functional groups demonstrates that it is a mild but effective reducing agent that will undoubtedly find further applications in cross-coupling reactions involving aldehydes.

Acknowledgment. S.F.P. is grateful to the National Institutes of Health (GM38735), the National Science Foundation for a Presidential Young Investigator Award (Grant No. CHE-8552735), Eli Lilly and Company, and Rohm and Haas Company for financial support.

Supplementary Material Available: A representative cross-coupling procedure, ^1H NMR, ^{13}C NMR, and FAB mass spectra, and elemental analyses data for compounds **2–5** and **8–13** (14 pages). Ordering information is given on any current masthead page.

(13) Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743.

(14) Assigning furanoside and pyranoside structures to **12** and **13**, respectively, is based on ^1H NMR decoupling experiments on acylated derivatives of these compounds. See the supplementary material for further details.

(15) Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. *Tetrahedron Lett.* **1979**, 3883.

(16) A crystalline *N*-benzoyl derivative (mp 109–110 °C) of methyl pyranoside **13** was prepared using steps 1 and 2 in the last equation in Scheme II (70% yield).

Antitumor Tetrahydroisoquinoline Alkaloids from the Colonial Ascidian *Ecteinascidia turbinata*

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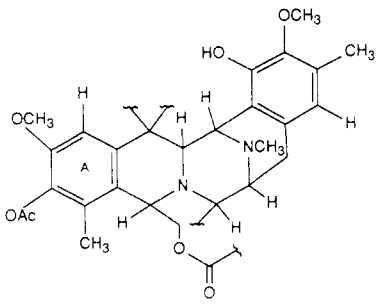
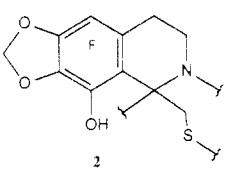
Received February 23, 1990

Summary: A bioassay guided approach was used to isolate two antitumor tetrahydroisoquinoline alkaloids, **3** and **4**, from the marine ascidian *Ecteinascidia turbinata*. The structures of **3** and **4** were determined through spectroscopic methods.

The crude aqueous ethanol extracts of the colonial ascidian *Ecteinascidia turbinata* were first reported to possess in vivo antitumor activity by Sigel et al. in 1969.[1] A number of research groups have been working on the isolation of the active constituents of the extract, most notably the researchers at the University of Illinois at Urbana–Champaign led by Professor Kenneth Rinehart.[2] In 1986, they suggested that the active compounds contained three tetrahydroisoquinoline rings.[2a] At a recent meeting[2b] they extended this analysis to partial structures **1** and **2** and suggested that the compounds are related to the safracin class of antitumor antibiotics. As part of our program to discover new antitumor agents, a butanol



1



2

partition of a crude methanol–toluene (3:1) extract of *E. turbinata* (8-V-85-3-9), collected near Ramrod Key in the Florida Keys in May 1985, was found to statistically prolong the life of mice infected with P388 murine leukemia by 45%. The isolation and structure elucidation of the active components was undertaken in 1986, and we now report in this paper our progress toward the structure elucidation of two active constituents of the extract. The compounds were isolated by repeated reversed-phase chromatography. The purification was followed by in vitro bioassay against a P388 murine leukemia tumor cell line. The structures of the compounds were determined through spectroscopic methods and were dependent upon the

(1) Sigel, M. M.; Wellham, L. L.; Lichter, W.; Dudeck, L. E.; Gargus, J. L.; Lucas, L. H. In *Food-Drugs From the Sea, Proceedings, 1969*; Youngken, H. W., Ed.; Marine Technology Society; Washington DC, 1970; pp 281–295.

(2) (a) Holt, T. G. Ph.D. Dissertation, University of Illinois, Urbana, 1986; *Chem. Abstr.* **1987**, *106*, 193149u. (b) Rinehart, K. L. 30th Ann. Mtg. Am. Soc. Pharmacognosy, San Juan, Puerto Rico, Aug. 6–10, 1989.

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