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DIASTEREOSELECTIVE ALKYLATION OF THE DIANION OF 5-ETHOXY-4(S)-HYDROXY-1-ISOPROPYL-2-PYRROLIDINONE; SYNTHESIS OF ENANTIOMERICALLY PURE AZABICYCLES

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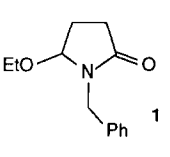
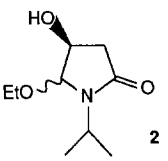
Abstract: The alkylation of the dianion of the title compound (2), readily prepared from (S)-malic acid, with ω-iodo-1-trimethylsilyl-2-alkynes (8a-c) occurs with high trans-selectivity with respect to the hydroxyl function. The products (11a-c) cyclize in formic acid to enantiomerically pure azabicyclic allenes (12a-c), one of which (12b) might be a suitable precursor to peduncularine (15).

5-Ethoxy-2-pyrrolidinone 1 is a dipolar synthon with a nucleophilic 3-position and an electrophilic 5-position, which has been shown to be useful for the synthesis of various azabicyclic molecules[1]. From the stereochemical point of view, 1 is less serviceable, since alkylation of its enolate leads to an approximately 1:1 mixture of stereoisomers, thus making enantiomerically pure 1, if available, useless as starting material[1a]. In this letter we wish to report that enantiomerically pure 2 readily available from (S)-malic acid, is in addition to its quality as dipolar synthon, an excellent chiral starting material.



1

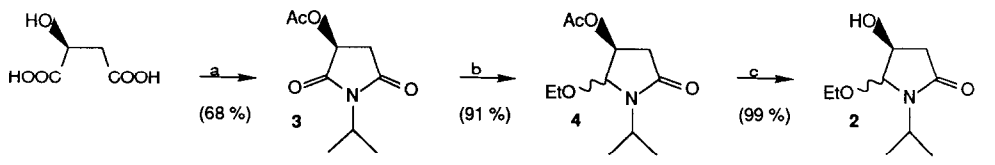


2

The synthesis of key molecule 2 is detailed in Scheme I. Treatment of (S)-malic acid with, successively, acetyl chloride, isopropylamine and again acetyl chloride[2] furnished imide 3 as a nicely crystalline solid[3]. Reduction of this imide with $NaBH_4$[2] occurred with virtually complete regioselectivity to a hydroxy lactam, which on ethanolysis afforded ethoxy lactam 4 as an epimeric mixture at C-5. Removal of the acetyl group proceeded in high yield to give the desired alcohol 2[3] as a 85:15 mixture of C-5 epimers.

Our basic strategy for the synthesis of azabicyclic systems from 2 (Scheme II) consists of, successively, deprotonation to dianion 5, alkylation to 6 and cyclization to 7. The deprotonation of 2 with 2.1 eq of lithium diisopropylamide (LDA) in THF to dianion 5 was allowed to occur at -78°C for 1 h and was then completed at -25°C for 1 h. Alkylation reactions of 5 with iodomethane, acetone and iodides 8a-c (See Table) proceeded with high stereoselectivity to the 3,4-trans-products 9[3], 10[3] and 11a-c[3], as no trace of 3,4-cis-products could be detected[4]. The trans-stereochemistry was not established at this stage, but after the subsequent cyclization

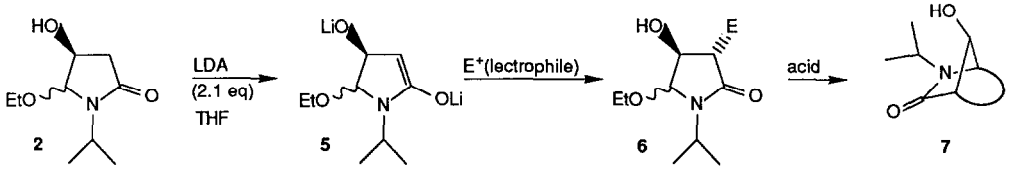
SCHEME I



a.1) 7.2 eq. AcCl, 1.5 h reflux 2) 2.6 eq. $iPrNH_2$, THF, r.t. 3) 7.2 eq. AcCl, 5 h reflux b. 1) 5 eq. $NaBH_4$, EtOH, 15 min. -15°C 2)2 N H_2SO_4/EtOH, 15 min. -25°C, 1 h r.t. c. NaOEt (cat.), EtOH.

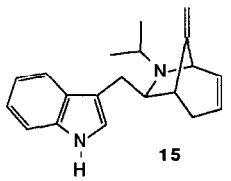
reaction (vide infra). The alkylation products were again 85:15 mixtures of C-5 epimers, indicating that the asymmetry at C-5 has no influence on the stereochemistry of alkylation. Elimination of HI which at -78°C lowered the yield of alkylation with iodide 8b, could be suppressed by carrying out the reaction at -117°C.

SCHEME II

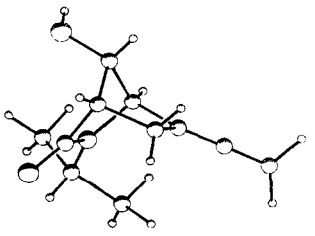


Cyclization experiments (6 → 7, Scheme II) were carried out by dissolving the alkylation products 11a-c in formic acid, and stirring the resulting solutions about 4 h at room temperature[5]. The products were mainly formate esters, which after evaporation of formic acid, were deformylated to the corresponding alcohols through treatment with methanolic ammonia. In this manner were obtained the crystalline allenes 12a-c[3] along with protodesilylation products 13a-c and their dimers 14a and 14c. Not surprisingly, 6-membered ring formation appeared to be the most facile reaction.

The relative stereochemistry of 12b and 12c was proved by using the NOE difference technique in ^{1}H NMR spectroscopy. Irradiation of the methine proton adjacent to the hydroxyl function led to a clear intensity enhancement of the signals of at least one of the methylene hydrogens in both compounds. An X-ray crystallographic analysis proved the structure of 12a (See Figure). These facts established the trans-stereochemistry of the alkyl substituent with respect to the hydroxyl function in 11a-c and by analogy in the other alkylation products 9 and 10.



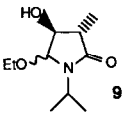
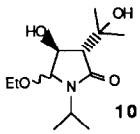
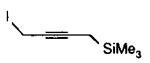
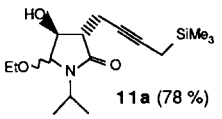
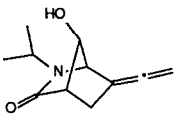
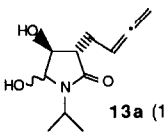
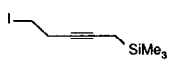
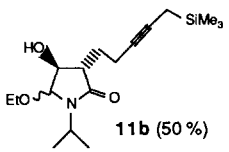
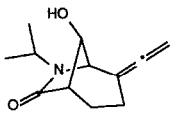
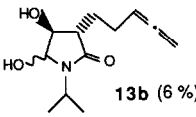
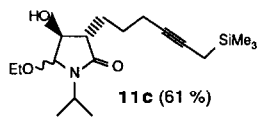
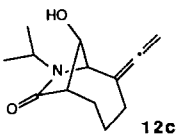
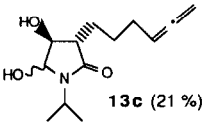
15



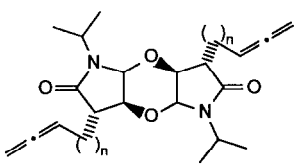
Figure

The enantiomerically pure bicyclic lactams 12a-c may be useful compounds for several purposes. Hydrolysis of the lactam function could lead to interesting γ-amino acids[8]. Removal of the carbonyl group will lead to amino alcohols, which could be applied in chiral base catalysis[9]. Our work is currently being directed towards the synthesis of peduncularine (15), an Aristotelia alkaloid of unknown absolute stereochemistry, which has shown antitumour activity[10,11]. Azabicyclic allene 12b seems to be a suitable precursor, since we have recently shown that an exocyclic allene can be readily transformed into an endocyclic olefin[1c,d]. Further studies will be reported in due course.

TABLE

electrophile (alkylation conditions)[c]	alkylation product[a] (isolated yield)	products[b] after cyclization and deformylation (isolated yield)
CH_3I (1 h, -78°C)	 **9** (69 %)	
$(CH_3)_2CO$ (3.5 h, -78°C)	 **10** (60 %)	
 **8a**[d] (6 h, -117°C)	 **11a** (78 %)	 **12a** (53 %)  **13a** (17 %) + dimer[e] **14a** (6 %)
 **8b**[d] (6 h, -117°C)	 **11b** (50 %)	 **12b** (87 %)  **13b** (6 %)
 **8c**[d] (3.5 h, -78°C)	 **11c** (61 %)	 **12c** (53 %)  **13c** (21 %) + dimer[e] **14c** (5 %)

a) About 85:15 mixture of C-5 epimers. b) For spectral data see ref. 12. c) After application of these conditions the reaction mixtures were allowed to slowly warm up to room temperature and then worked up. d) This iodide was prepared by treating the mesylate of the corresponding alcohol[6,7] with 3 eq of KI in DMF. e) The structure of this compound is:



14a n = 1
14c n = 3

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2. For a similar sequence see: a) A.R. Chamberlin, Y.L. Chung, J.Am.Chem.Soc., 105, 3653 (1983); b) D.J. Hart, T.-K. Yang, J.Org.Chem., 50, 235 (1985).
3. This compound showed spectra (IR, ^{1}H NMR, ^{13}C NMR)[12] in accord with its structure, and satisfactory combustion analyses and/or high resolution mass spectral data.
4. For similar results in the case of β-hydroxylactone dianions see: a) H.-M. Shieh, G.D. Prestwich, J.Org.Chem., 46, 4319 (1981); b) A.R. Chamberlin, M. Dezube, Tetrahedron Lett., 23, 3055 (1982); c) D. Seebach, H-F. Chow, R. Jackson, K. Lawson, M.A. Sutter, S. Thaisrivongs, J. Zimmermann, J.Am.Chem.Soc., 107, 5292 (1985). See also: d) G.J. McGarvey, J.M. Williams, R.N. Hiner, Y. Matsubara, T. Oh, Ibid, 108, 4943 (1986); e) P. Renaud, D. Seebach, Synthesis, 424 (1986).
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8. See e.g.: R.D. Allan, G.A.R. Johnston, Med.Res.Rev., 3, 91 (1983).
9. See e.g. a) H. Hiemstra, H. Wynberg, J.Am.Chem.Soc., 103, 417 (1981); b) R.J. Vijn, W.N. Speckamp, B.S. de Jong, H. Hiemstra, Angew.Chem.Int.Ed.Engl., 23, 165 (1984).
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11. a) H.-P. Ros, R. Kyburz, N.W. Preston, R.T. Gallagher, I.R.C. Bick, M. Hesse, Helv.Chim. Acta, 62, 481 (1979); b) I.R.C. Bick, M.A. Hai, N.W. Preston, Tetrahedron, 41, 3127 (1985).
12. Some selected data are as follows: 12a: mp. 95-8°C; $[\alpha]_D^{20}$+306° (c=0.87, $CHCl_3$); IR($CHCl_3$): 3350 (br), 1965, 1675 cm^{-1}; ^{1}H NMR($CDCl_3$, 200 MHz) δ 5.05 (br, OH), 4.75 (m, $C=CH_2$), 4.17 (s, J=7 Hz, $CH(CH_3)_2$), 4.04 (m, CHOH & NCH), 2.68 (m, COCH), 2.60 (m, 1H), 2.23 (m, 1H), 1.15 (d, J=7 Hz, $CHCH_3$), 1.03 (d, J=7 Hz, $CHCH_3$); ^{13}C NMR($CDCl_3$, 50 MHz) δ 201.7 (s), 174.7 (s), 98.2 (s), 79.4 (d), 77.9 (t), 65.2 (d), 50.9 (d), 42.6 (d), 28.0 (t), 20.9 (q), 20.5 (q). 12b: mp. 147-9°C; $[\alpha]_D^{20}$+258° (c=5.04, $CHCl_3$); IR($CHCl_3$): 3370 (br), 1965, 1680 cm^{-1}; ^{1}H NMR($CDCl_3$, 200 MHz) δ 4.72 (m, $C=CH_2$), 4.34 (s, J=7 Hz, $CH(CH_3)_2$), 4.11 (s, NCH), 3.89 (s, CHOH), 3.10 (br, OH), 2.53 (m, COCH), 2.20 (m, 2H), 1.99 (m, 1H), 1.68 (m, 1H), 1.18 (d, J=7 Hz, $CHCH_3$), 1.15 (d, J=7 Hz, $CHCH_3$); ^{13}C NMR($CDCl_3$, 50 MHz) δ 202.5 (s), 174.1 (s), 98.5 (s), 77.9 (d), 75.7 (t), 63.6 (d), 49.3 (d), 43.1 (d), 23.8 (t), 22.5 (t), 20.2 (q), 20.0 (q). 12c: mp. 102-5°C; $[\alpha]_D^{20}$+161° (c=0.15, $CHCl_3$); IR($CHCl_3$): 3370 (br), 1950, 1660 cm^{-1}; ^{1}H NMR($CDCl_3$, 250 MHz) δ 4.66 (m, $C=CH_2$), 4.24 (s, NCH), 4.20 (s, J=7 Hz, $CH(CH_3)_2$), 4.12 (s, CHOH), 3.16 (br, OH), 2.52 (m, COCH), 2.23 (m, 2H), 1.99 (m, 1H), 1.63 (m, 3H), 1.22 (d, J=7 Hz, $CHCH_3$), 1.17 (d, J=7 Hz, $CHCH_3$).

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