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A CONVENIENT SYNTHESIS OF REGIO-SPECIFICALLY 2-ALKYLATED-3-DEUTERIATED-1-AMINOCYCLOPROPANE-1-CARBOXYLIC ACIDS

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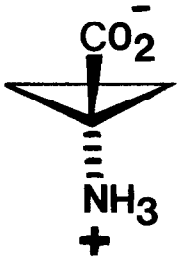
Abstract - A simple procedure for the large scale preparations of regio-specifically 2-alkylated-3-deuteriated-1-aminocyclopropane-1-carboxylic acids from 1-deuterio-1,2-dibromoalkanes is described.

During the course of our continuing studies into the biosynthesis of ethylene from 1-aminocyclopropane-1-carboxylic acid [1,2](ACC) 1 we have required a convenient synthesis of regiospecifically alkylated and deuteriated ACC derivatives (e.g. 2,3). As the existing procedures for the synthesis of coronamic acid 2e [3,4] and allocoronamic acid 3e [5] would not allow specific deuteriation at C(3) of the cyclopropane ring, an alternative and more general route, capable of large scale preparations was sought.



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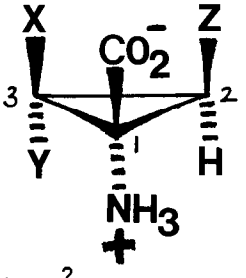
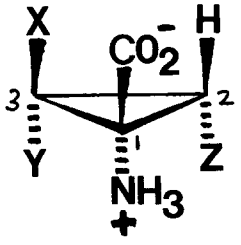
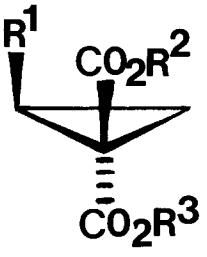


2 a) X = ^{2}H, Y = H, Z = Me
b) X = H, Y = ^{2}H, Z = Me
c) X = ^{2}H, Y = H, Z = Et
d) X = H, Y = ^{2}H, Z = Et
e) X = Y = H, Z = Et
f) X = Y = H, Z = Me



3 a) X = ^{2}H, Y = H, Z = Me
b) X = H, Y = ^{2}H, Z = Me
c) X = ^{2}H, Y = H, Z = Et
d) X = H, Y = ^{2}H, Z = Et
e) X = Y = H, Z = Et
f) X = Y = H, Z = Me

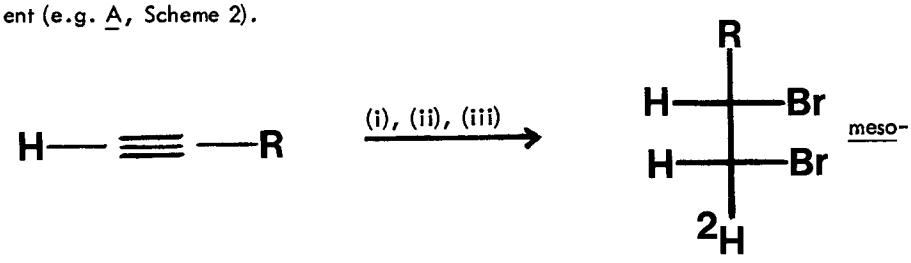


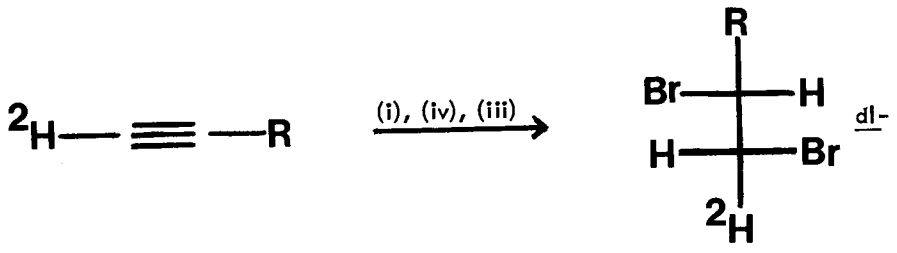
4 a) R^1 = Me, R^2 = R^3 = Bu^t
b) R^1 = Et, R^2 = R^3 = Bu^t

5 a) R^1 = R^2 = R^3 = Me
b) R^1 = Et, R^2 = R^3 = Me

6 a) R^1 = R^2 = Me, R^3 = K
b) R^1 = Et, R^2 = Me, R^3 = K
c) R^1 = R^3 = Me, R^2 = K
d) R^1 = Me, R^2 = R^3 = K

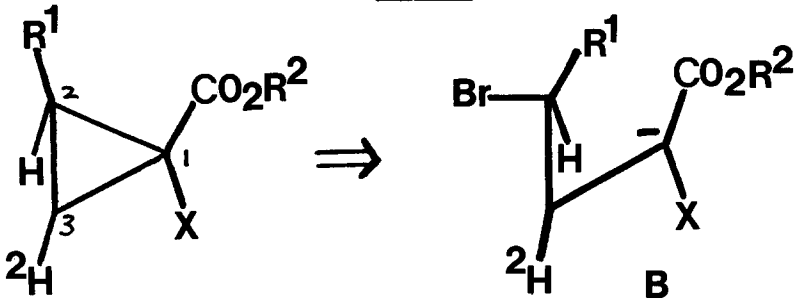
The ready availability of meso- and dl-1-deuterio-1,2-dibromoalkanes (Scheme 1) made them suitable synthons for C(2) and C(3) of the cyclopropane ring, the ring forming reaction thus requiring a glycine dianion equivalent (e.g. A, Scheme 2).

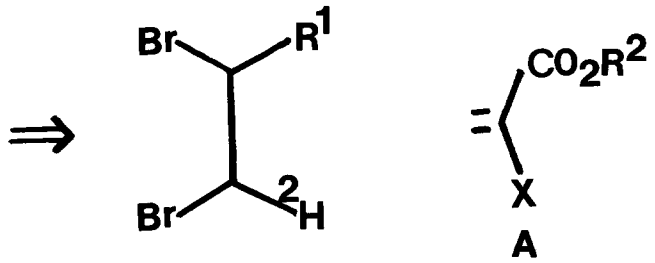




Reagent: (i) Disiamylborane; (ii) ^{2}HOAc; (iii) Br_2, KBr (aq.), 0°C, "trans addition"; (iv) HOAc.

Scheme 1





X = $-CO_2R^2$, $-N=C(H)(Ph)$, etc

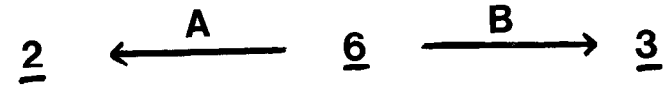
R^1 = alkyl

Scheme 2

Danishefsky has reported[6] a modification of the classical Perkin synthesis of cyclopropane-1,1-dicarboxylate [from diethyl malonate and ethylene dibromide] using phase transfer catalysis conditions [triethylbenzylammonium chloride (TEBA), 50% (w/v) sodium hydroxide as base] which leads to a 75% yield of cyclopropane-1,1-dicarboxylic acid. However in our hands, both the classical Perkin procedure (which is known to be more difficult when displacements of an unactivated secondary bromide is required[7]) and the phase transfer catalysis conditions of Danishefsky gave very low yields of the cyclopropane from 1,2-dibromopropane and diethyl malonate. A similar failure, under these phase transfer conditions, for the preparation of 1-amino-2-ethylcyclopropane-1-carboxylic acid from the benzophenone imine of aminoacetonitrile and 1,2-dibromobutane was observed by O'Donnell.[8]

The success of Danishefsky's ring forming procedure lies in ring formation prior to ester hydrolysis. We argued that providing ester hydrolysis was suppressed then ring formation *via* an intramolecular displacement of a secondary bromide[9] (e.g. B, Scheme 2) may occur. Thus treatment of a pre-formed mixture of 1,2-dibromopropane or 1,2-dibromobutane (0.15 mols.) and di-*tert*-butyl malonate (0.10 mols.), with TEBA (0.10 mols.) and sodium hydroxide (50% w/v, 2.50 mols.) at 20°C for 15h, gave upon extraction into dichloromethane, 2-methylcyclopropane-1,1-dicarboxylic acid, di-*tert*-butyl ester[10] 4a (76%) and 2-ethylcyclopropane-1,1-dicarboxylic acid, di-*tert*-butyl ester 4b (72%) respectively, in essentially pure form.[11]

In order to complete an amino-acid synthesis from 4a or 4b, selective differentiation of the two carboxylate functions must be made. Thus treatment of the dimethyl ester derivatives 5a and 5b (prepared in essentially quantitative yield from treatment of 4a or 4b with trifluoroacetic acid and diazomethane in sequence) with potassium hydroxide (1.4 equivs.) in methanol gave selective hydrolysis[12] of the less hindered ester function *trans*- to the 2-alkyl substituent to yield the carboxylate salts 6a and 6b. Transformation of these salts into regiospecifically alkylated ACC's followed from standard manipulations of either the carboxylic acid or ester functions to an amino group. Thus treatment of 6a and 6b via sequence A, scheme 3 gave (1R, 2R - and 1S, 2S)-2-methyl-1-aminocyclopropane-1-carboxylic acid 2f (43% from 5a), δH[13] 0.97(3H, d, J 6Hz, 2-Me), 1.00-1.11(2H, m, 3-H), 1.24-1.37(1H, m, 2-H) p.p.m., and (1R, 2R - and 1S, 2S)-2-ethyl-1-aminocyclopropane-1-carboxylic acid 2e[3,4] (47% from 5b), δH 0.70(3H, t, J 7Hz, CH_3CH_2), 1.07$_5$(2H, ca d, J 8Hz, 3-H), 1.20-1.44(3H, m, 2-H, CH_2CH_3) respectively, whereas via sequence B, Scheme 3, they gave (1R, 2S - and 1S, 2R)-2-methyl-1-aminocyclopropane-1-carboxylic acid 3f (32% from 5a), δH 0.68(1H, dd, J 6, 7.5Hz, 3-H), 0.99(3H, d, J 6.5Hz, 2-Me), 1.24(1H, dd, J 6, 9.5Hz, 3-H), 1.40-1.52(1H, m, 2-H), and (1R, 2S - and 1S, 2R)-2-ethyl-1-aminocyclopropane-1-carboxylic acid 3e[5] (41% from 5b), δH 0.70(1H, ca t, J 6.5Hz, 3-H), 0.84(3H, t, J 7Hz, CH_3CH_2), 1.07-1.45(4H, m, 2,3-H, CH_2CH_3) respectively.[14]



Reagents:

A: 2M HCl, extract into EtOAc; (ii) $NEt(Pr^i)_2$ (2 equivs.), EtO.CO.Cl (3 equivs.), acetone, 0°, 30 min.; (iii) NaN_3 (5 equivs.) in H_2O, 0°; (iv) reflux in toluene, 30 min; (v) 6M HCl, reflux, 6h.; (vi) Dowex 50W X 8 (H) ion exchange; (vii) recrystallisation (H_2O/acetone).

B: (i) $N_2H_4.H_2O$ (excess), EtOH, reflux, 12h.; (ii) $NaNO_2$ (1.5 equivs.), HCl, 0°, 2h.; then (iv) - (vii) as for sequence A.

Scheme 3.

A repeated synthesis from meso-1-deuterio-1,2-dibromopropane (via sequence B, Scheme 3) gave (1R, 2S, 3R- and 1S, 2R, 3S)-3-deuterio-2-methyl-1-aminocyclopropane-1-carboxylic acid 3b, δH 1.23(1H, d, J 9.5Hz, 3-H), whereas with dl-1-deuterio-1,2-dibromopropane (again via sequence B, scheme 3) (1R, 2S, 3S - and 1S, 2R, 3R)-3-deuterio-2-methyl-1-aminocyclopropane-1-carboxylic acid 3a, δH 0.67(1H, d, J 7.5Hz, 3-H) resulted.[15] By these means, the specifically C(2) alkylated and C(3) deuteriated aminoacids 2a - 2d and 3c, 3d were also prepared. Thus both the bromide displacements to form the cyclopropane ring occured by classical S_N2 Walden inversion pathways, and there was no loss of ring stereochemistry during the subsequent manipulations to the aminoacids.

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9. This procedure failed to give a cyclopropane from 2,3-dibromobutane.

10. All new compounds gave satisfactory analytical and spectral data.

11. An excess of 1,2-dibromoalkane (1.5 equivs.) was used to completely react the di-tert-butyl malonate as this is typically the most tedious to remove from a malonate based synthesis. After work up, residual TEBA was removed by filtration through silica gel.

12. When potassium hydroxide (1.25 equivs.) was used with 5a, then the ratio of 6a : 6c was 9:1. With KOH (1.4 equivs.), the major impurity of 6a was the symmetrical di-carboxylate salt 6d.

13. N.M.R. spectra recorded at 300MHz in D_2O solution using internal dioxan = 3.53 p.p.m. as reference.

14. Details of the resolution of 2f, 3e, and 3f will appear elsewhere.

15. The samples of 3b thus prepared was pure of 3a (and vice versa) as judged by ^1H, ^2H, and ^{13}C N.M.R. spectroscopy. The structure as 3a as the trans- C(2), C(3) isomer and 3b as the cis-C(2), C(3) isomer was proven by n.O.e. experiments. Thus irradiation of the C(2) methyl group of 3a gave a n.O.e. (5%) to 3-H, whereas irradiation of the C(2) methyl group of 3b gave no n.O.e. to 3-H.

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