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Asymmetric Synthesis of the Natural Diastereoisomer of *trans*-α-(2-Carboxymethylcyclopropyl)glycine isolated from *Blighia unijugata*

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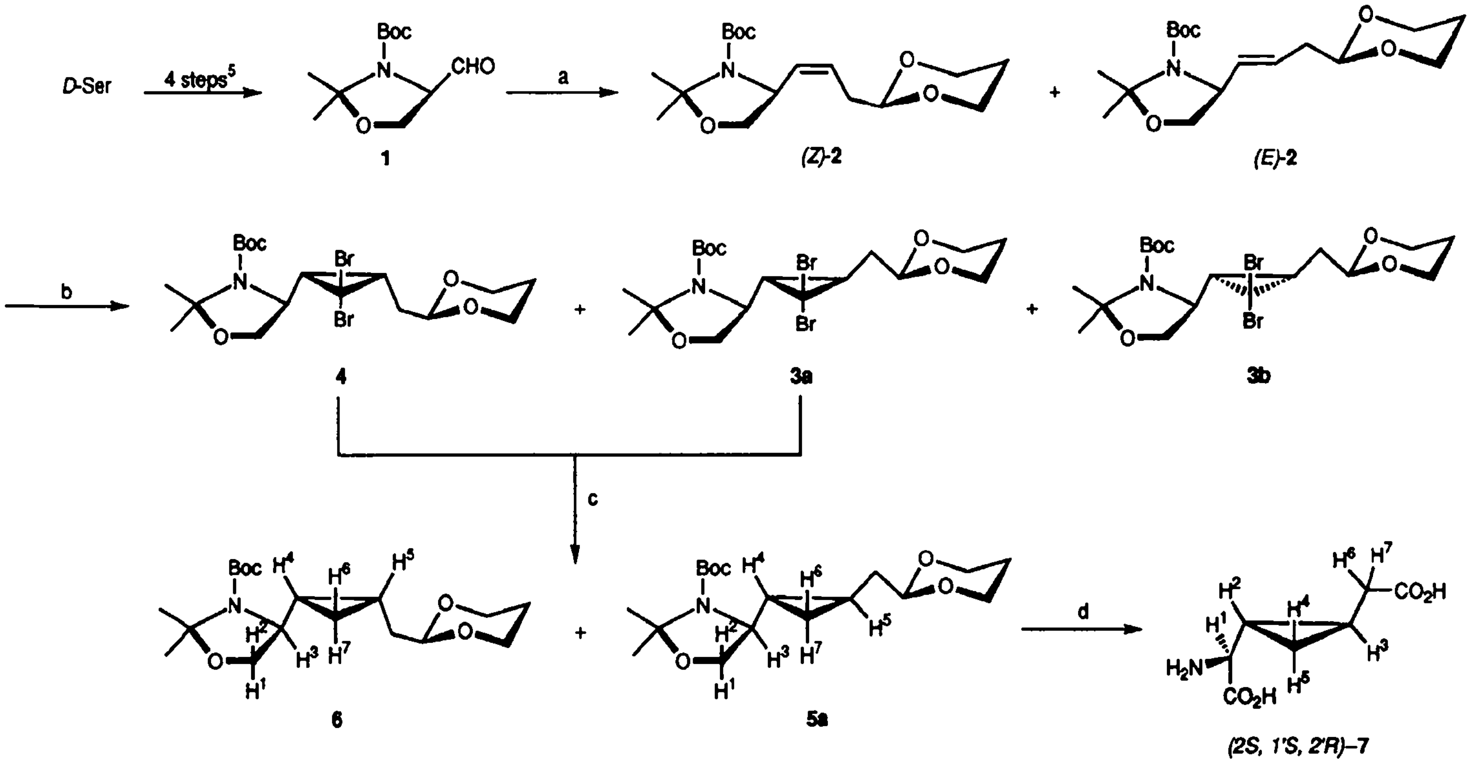
Abstract: An asymmetric synthesis of *(2S, 1'S, 2'R)*-α–(2-carboxymethylcyclopropyl)glycine, formerly isolated from *Blighia unijugata* is reported. The key step is the dibromocyclopropanation of the oxazolidine alkenes **2**, prepared in five steps from *D*-serine, which takes place with good diastereoisomeric ratios. The major dibromocyclopropane was reduced to the corresponding cyclopropane, which was transformed in a single step into the title cyclopropylglycine.

Recently a number of new amino acids have been discovered in nature.[1] Among them, those containing a cyclopropane ring have attracted special attention due to their biological activities as phytochemical agents, enzyme inhibitors or probes in metabolism studies.[2]

Cyclopropylglycines form the largest group of naturally occurring cyclopropane amino acids, but only a few papers have been published on their synthesis,[3] mainly referring to the synthesis of α-(methylenecyclopropyl)glycine and α-(2-carboxycyclopropyl)glycine. We have recently described the asymmetric synthesis of (*E*)-α-[2-phenyl(ethyl)cyclopropyl]glycines[3l] from serine by diastereoselective dibromocyclopropanation, and we report now on the asymmetric synthesis of *trans*–α–(2-carboxymethylcyclopropyl)glycine, a natural product first isolated from the seeds of *Blighia unijugata*,[4] which is a homolog of *trans*–α–(2-carboxycyclopropyl)glycine, known as a NMDA receptor agonist.

The oxazolidine aldehyde **1** was easily prepared in four steps from *D*-Serine in 65% overall yield.[5] Wittig reaction of this aldehyde with the ylide derived from 2-(1,3-dioxan-2-yl)ethylidenetriphenyl phosphonium bromide[6] by treatment with sodium hydride, gave a 80:20 mixture of *Z* and *E* alkenes **2** (Scheme 1). The major alkene was assumed to have *Z* configuration, the preferred one in this reaction with non-stabilized ylides.[7]

The mixture of alkenes **2** was refluxed with N-bromosuccinimide in benzene to produce a 66:33 mixture of both alkenes, which could not be separated by chromatography.



Scheme 1. *Reagents*: (a) 2-(1,3-dioxan-2-yl)ethylidenetriphenylphosphonium bromide, 95% HNa, THF (argon), r.t., 2h.
(b) $CHBr_3$, KOH (s), TEBA, benzene, t < 30 °C,))), 18h.
(c) *n*-Bu_3SnH, hexane (argon), reflux, 24h.
(d) 1. CrO_3, H_2SO_4, acetone-H_2O, r.t., 3h. 2. Dowex 50W (H^+ form)

Addition of dibromocarbene, generated by the phase-transfer catalytic technique,[8] to the mixture of alkenes **2** (*Z*/*E* = 2/1) gave, after 10-15 days, a mixture of two dibromocyclopropyl derivatives, both of them having *trans*-relative configuration. An isomerization of *Z*- to *E*-alkene took first place and dibromocarbene was exclusively added to the *E*-isomer in a good diastereoisomeric ratio (**3a**/**3b** = 4/1), although in poor yield (20%).

It has been described that reaction times and yields in the addition of dichlorocarbene to olefins when this is generated under sonication, compare favorably with analogous phase-transfer procedures.[9] In our case, when the addition of dibromocarbene to alkenes **2** was carried out with efficient stirring and ultrasonic irradiation, using a large excess (10 equivalents) of powdered potassium hydroxide and bromoform and a catalytic amount of triethylbenzylammonium chloride, a mixture of dibromocyclopropanes was obtained in 73% yield. The use of the phase-transfer catalyst was not strictly necessary, but the addition was faster in its presence. Under these conditions a mixture of three bromides (**3a**:**3b**:**4**) in a 4:1:2 ratio was obtained. One of the dibromocyclopropanes, compound **4**, possesses *cis*-relative configuration, in contrast with results obtained without sonication. The facial stereoselectivity in the dibromocyclopropanation of *E*-alkene is the same in both cases.

The two major compounds (**3a**/**4** = 2/1) refused to be separated by chromatographic means hence the mixture of both was reduced with two molar equivalents of tributyltin hydride to give the corresponding cyclopropanes **5a** and **6** (85%), which were easily separated by flash chromatography.

Structural analyses were carried out for compounds **5a** and **6** on the basis of 1D and 2D ^{1}H-NMR spectroscopic data in order to determine their relative configurations. Thus, analysis of the ^{1}H-NMR spectra of compounds **5a** and **6** using the PANIC program gave the relevant coupling constants shown in Table 1. The values of the coupling constants of the geminal protons H-6 and H-7 (see Scheme 1) with the cyclopropane protons H-4 and H-5 indicate a *trans* configuration for compound **5a** and a *cis* configuration for **6**. On the other hand, the large coupling constant of 8.4 Hz suggests a dihedral angle of about 170° between protons H-3 and H-4 in **5a**.

Table 1. Relevant Vicinal Coupling Constants (^3J, Hz) found for Compounds **5a** and **6**

Comp.	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,6}$	$J_{4,7}$	$J_{5,6}$	$J_{5,7}$	$J_{6,7}$
5a	-9.0	5.6	1.1	8.4	4.3	8.4	4.6	4.7	8.5	-4.9
6	-8.7	5.6	2.0	8.8	8.6	8.7	5.9	8.6	5.9	-4.8

The 2D-NOESY spectra of compound **5a** show, in addition to the expected H-4/H-6, H-5/H-7, H-3/H-5 and H-3/H-7 crosspeaks, which strongly support the *trans* configuration of the cyclopropane ring, a crosspeak H-2/H-7 which, in conjunction with the value of $J_{3,4}$, suggests a configuration 1'S, 2'R for the cyclopropane moiety, as depicted in Scheme 1.

Compound **5a** was treated with Jones' reagent to give, after ion exchange chromatography, 75% of the natural *trans*-2-(2'-carboxymethylcyclopropyl)glycine (**7**)[10]: $[\alpha]_D$ +13 (*c* 0.67, H_2O), lit.[4] $[\alpha]_D$ +12 (*c* 1, H_2O).

A previous synthesis of compound **7**, starting from *L*-serine, gave an absolute value of $[\alpha]_D$ equal to that of the natural compound but with opposite sign. Thus, we propose an absolute configuration 2S, 1'S, 2'R for the natural diastereoisomer of compound **7**. Unfortunately an authentic sample was not available.

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10. ^{1}H-NMR (D_2O, 30 °C) (analysed by the PANIC program): δ 3.159 (d, $J_{1,2} = 9.9$, H-1), 2.504 (dd, $J_{3,7} = 6.3$, $J_{6,7} = -17.2$, H-7), 2.241 (dd, $J_{3,6} = 8.2$, $J_{6,7} = -17.2$, H-6), 1,123 (m, $J_{2,3} = 4.4$, $J_{3,4} = 8.6$, $J_{3,5} = 5.3$, $J_{3,6} = 8.2$, $J_{3,7} = 6.3$, H-3), 1.103 (m, $J_{1,2} = 9.9$, $J_{2,3} = 4.4$, $J_{2,4} = 5.2$, $J_{2,5} = 8.9$, H-2), 0.930 (dt, $J_{2,5} = 8.9$, $J_{3,5} = 5.3$, $J_{4,5} = -5.5$, H-5), 0.753 (dt, $J_{2,4} = 5.2$, $J_{3,4} = 8.6$, $J_{4,5} = -5.5$, H-4).

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