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Asymmetric Syntheses of 1-Amino-2-Phenyl(Alkyl)cyclopropanecarboxylic Acids by Diastereoselective Cyclopropanation of Highly Functionalized Monochiral Olefines[1#]

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Abstract: Monochiral α-benzamidocinnamic esters of N-methylephedrine or mandelic derivatives and benzylidene or alkylidene diketopiperazines, all obtained from oxazolones, react with diazomethane to give moderate to high diastereomeric excesses (d.e.) of pyrazoline derivatives which, after photolysis and acid hydrolysis of the resulting cyclopropyl compounds, gave (1*R*, 2*R*)- , (1*S*, 2*S*)- or *(1S, 2R)*-1-amino-2-phenyl(alkyl)cyclopropanecarboxylic acids. The enantiomerically pure dipeptide of the (1*R*, 2*R*) enantiomer with *S*-proline was also obtained by selective cleavage of the diketopiperazine moiety. The structure of all compounds has been assessed by NMR studies and by X-ray crystallography analysis of an intermediate spiroderivative.

INTRODUCTION

1-Amino-1-cyclopropanecarboxylic acids (ACC) attract special attention, due to their diverse documented biological activities.[2] Several procedures for the preparation of this class of aminoacids have been described.[2-9] Obviously, due to the strict stereochemical requisites of biological receptors, it is necessary to obtain pure enantiomers for studying biological interactions. Most of the reported optically pure enantiomers of cyclopropane amino acids have been produced by resolution of racemic mixtures.[10] The first asymmetric synthesis of a ACC was published by Pirrung *et al*[11] for (1*R*, 2*S*) and (1*S*, 2*R*)-2-methyl ACC. Marco[12] prepared (1*S*, 2*R*)-2-ethyl ACC (allocoronamic acid) although in low yield and moderate optical purity. Pirrung[13] reported the preparation of (1*R*, 2*S*)- and (1*S*, 2*R*)-2-hydroxymethyl ACC, while Husson *et al*[14] described the synthesis of (1*S*, 2*R*) and (1*S*, 2*S*) diastereoisomers of the same compound, by two independent procedures. Schöllkopf[15] proposed the use of a chiral bislactim ether carbene, which apparently may be applied to the asymmetric synthesis of this kind of compounds, but has been employed so far to prepare a *meso*-2,3-disubstituted ACC. Salaün *et al*[16] have synthesized (1*S*, 2*S*)-2-methyl ACC (norcoronamic acid) by transformation of *(S)*-methyl 3-hydroxy-2-methylpropionate, and Viallefont et al[17] have described the preparation of (1*S*, 2*R*) and (1*R*, 2*R*)-2-methyl ACC, starting from alkylidene derivatives of a cyclic glycine-condensed pinanone, but the stereocontrol of the reaction is low and unresolved mixtures of coronamic and allocoronamic acids are produced when the propylidene derivative is used as starting material. Williams *et al* have reported[18] on the synthesis of coronamic

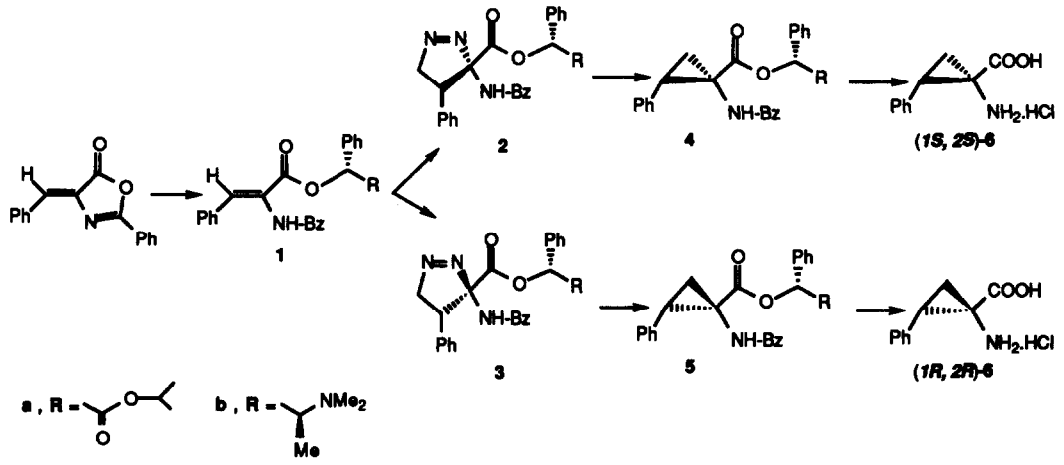
Dedicated to Prof. E. Fernández-Alvarez on occasion of his 65th birthday

and norcoronamic acids by using chiral diphenyl-1,4-oxazine derivatives. Burgess *et al*[19] synthesized cyclopropane analogs of ornitine, arginine and methionine and finally, de Meijere and Meyers[20] the preparation of 2-substituted 1-aminocyclopropanecarboxylic acids in optically pure form. It seems evident that finding inexpensive and general synthetic methods for obtaining enantiomerically pure forms of these compounds is still convenient.

We have reported a simple method to obtain racemic (*Z*)- and (*E*)-1-amino-2-aryl(alkyl)cyclopropanecarboxylic acids, starting from inexpensive 4-arylideneoxazolones.[3] This still appeared a convenient approach for asymmetric synthesis, provided pertinent modifications of the starting syntons were made in order to introduce in the molecule monochiral groups which might induce asymmetric cyclopropanation, the key step in the process.[1]

RESULTS AND DISCUSSION

Cleavage of *(Z)*-2-phenyl-4-benzylideneoxazolone with (*R*)-isopropyl mandelate in the presence of *p*-toluenesulfonic acid or N-methylephedrine with sodium hydride gave good yields of the corresponding α-benzamidocinnamates **1** (Scheme 1). Diastereoselective cyclopropanation of these compounds was performed *via* 1,3-dipolar cycloaddition of diazomethane at 0 °C to give diastereomeric mixtures of the corresponding pyrazolines **2** + **3**. The diastereomeric ratios (60 : 40 and 65 : 35, respectively) were determined on the crude mixtures by ^{1}H-NMR analysis. Early attempts with lactate derivatives and mandelic esters other than the isopropyl compound gave poorer results.

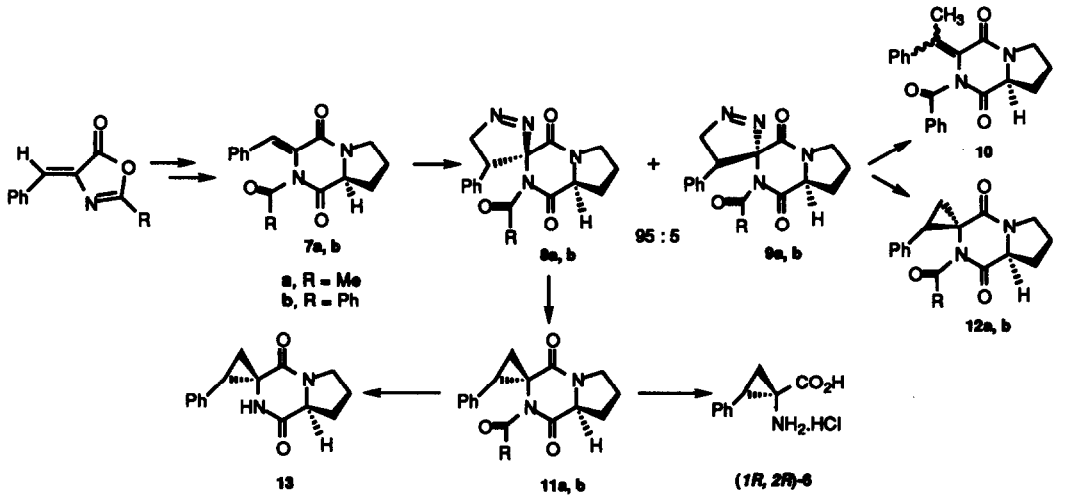


Scheme 1

Photolytic decomposition of **2a** and **3a**, which were isolated by flash chromatography, produced the respective cyclopropyl compounds **4a** and **5a**. Acid hydrolysis of those gave the desired phenylcyclopropyl aminoacids (1*S*, 2*S*)-**6** and (1*R*, 2*R*)-**6**. Attempts to isolate **2b** and **3b** led to isomerization to Δ^2 pyrazolines. As an alternative, the mixture of Δ^1 pyrazolines was photolytically converted into a diastereomeric mixture of the cyclopropyl derivatives **4b** and **5b** which were then separated by flash chromatography. Hydrolysis of the major compound (**4b**) led to aminoacid (1*S*, 2*S*)-**6**, identical to that obtained from **4a**.

The absolute configuration of all these compounds were deduced on comparison with those obtained from compounds **11a** and **13** (see below).

Searching for better diastereoselectivity we further studied cyclopropanation of the rigid diketopyperazines **7a,b** (Scheme 2), also obtained by cleavage of the corresponding oxazolones with *S*-proline and further cyclization of the resulting α-acylaminocinnamates.[21] Addition of diazomethane to those products gave compounds **8a,b** and **9a,b** in diastereomeric ratios > 95 : 5. Photolysis of **8a** under the usual conditions afforded the spiroderivative **11a** (90%), while analogous treatment on **8b** produced a mixture of compounds, from which **11b** was isolated in 25% yield. The minor diastereoisomer **9a** was isolated from the mother liquors after crystallization of **8a**, and was also photolyzed to give **12a**. On the other hand, a mixture of compounds **12b** (25%) and **10** (25%) was obtained by refluxing **9b** in toluene. Although the yield is similar to that obtained by photolysis, isolation of the spirocyclopropane was easier, since pyrolysis produced much less byproducts than photolysis in this case.

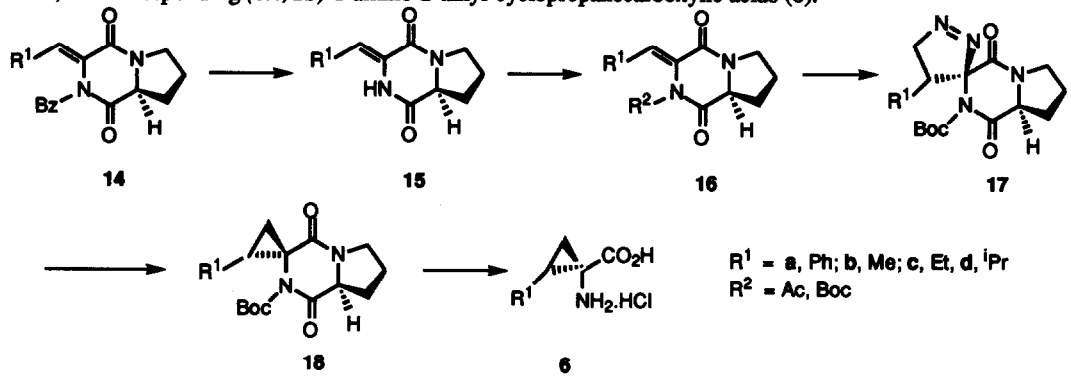


Scheme 2

Acidic hydrolysis of **11a** gave 75% of aminoacid (1*R*, 2*R*)-**6**, together with a small amount of stiryl glicine.[22] Deacetylation of the major spiroderivative **11a** under smooth acidic conditions led to **13**, which was used for X-ray studies (see below).

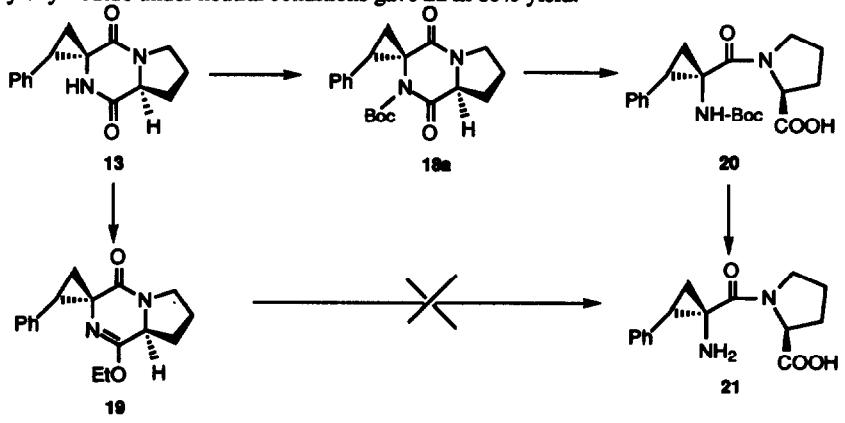
In order to synthesize the more appealing alkylcyclopropanecarboxylic acids, some *(Z)*-2-phenyl-4-alkylidene-5(4H)-oxazolones were prepared by known methods[23] and Schmidt's procedure[21] was used to convert them into the corresponding diketopiperazines **14** (Scheme 3). As in the case of the benzylidene derivative, addition of diazomethane gave the corresponding pyrazolines, but problems arose again in the photolytic reaction of these compounds, which led to complex mixtures of products. The change of the protecting group seemed advisable; so we first obtained compounds **15** by reacting the appropriate derivative **14** with glycine-methyl ester hydrochloride and triethylamine.[21] The synthesis of the N-acetyl derivatives (**16**; R^2 = Ac) was first attempted but these compounds were unstable. Finally, N-(*tert*-butoxycarbonyl)-diketopiperazines (**16**; R^2 = Boc) were synthesized in good yiels by treatment of **15** with di-*tert*-butyl dicarbonate, 4-dimethylaminopyridine and triethylamine. Diketopiperazines **16** were then reacted with diazomethane, followed

by photolytic treatment to produce monochiral spirocyclopropanes **18**. Acid hydrolysis of the last gave, after removing the starting *S*-proline through an ion-exchange column[24] and recrystallization from ethanol/diethyl ether, the corresponding *(1R, 2S)*-1-amino-2-alkyl-cyclopropanecarboxylic acids (**6**).



Scheme 3

We further tried to obtain the peptide **21** (Scheme 4), for which we attempted to selectively split the peptidic bond with the secondary nitrogen in **13**. Kinetic studies on the hydrolysis of diketopiperazines have shown[25] the difficulties of such selective splitting. After unfruitful attempts under both acidic and basic conditions we decided to prepare the ethoxy derivative **19**, which was easily achieved in 90% yield by treatment of **13** with F_4BOEt_3 (Scheme 4). However, acid hydrolysis of **19** led to recovery of diketopiperazine **13**, while mild basic reaction with potassiun carbonate gave unchanged **19**. As an alternative, compound **18a** was carefully hydrolyzed with 1N NaOH to give 90% of the protected dipeptide **20**, no epimerization in the proline moiety was observed. Attempted acid hydrolysis or thermal elimination of the protecting group in the last derivative led only to cyclization to the starting material **13**. However, treatment of **20** with *tert*-butyldimethylsilyl iodide under neutral conditions gave **21** in 60% yield.

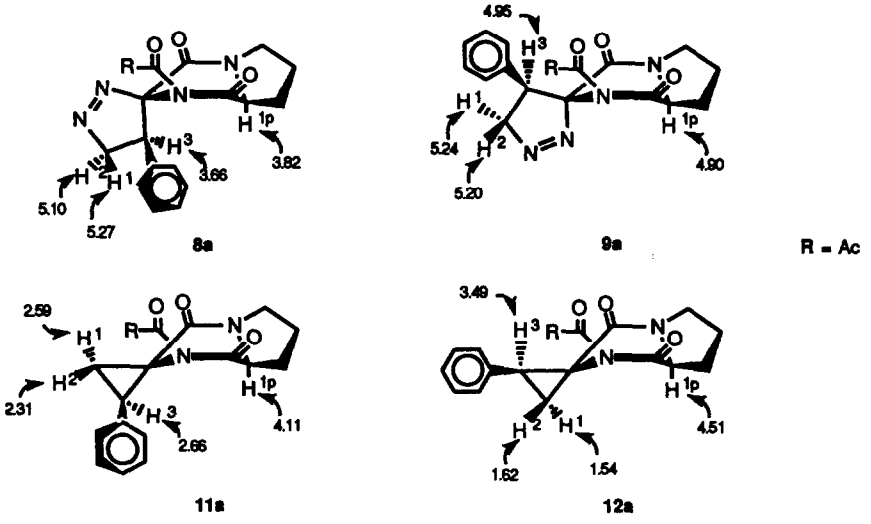


Scheme 4

Structural features

The absolute configuration of all compounds was established by comparison with derivatives **8a**, **9a**, **11a**, **12a**, **13**, and literature $[\alpha]_D$ values[27] of the final ACC.

The ^{1}H-NMR values for compounds **8 - 12** were optimized with the iterative program PANIC. Relevant ^{1}H-NMR values (ppm) for **8a, 9a, 11a,** and **12a** are shown below:



Assuming that 1,3-dipolar cycloaddition must take place mainly on the less hindered face, the major compound should have structure **8a** and the minor one the configuration **9a**. This assumption is supported by the chemical shift values of H-3, strongly deshielded in **9a**, as compared with those in **8a**, because of the proximity of the C = O group in the former. In addition, the proton on the chiral center of the proline moiety (H-1p) is strongly shielded in compound **8a** ($\Delta\delta$ = -1 ppm as compared with **9a**) probably due to the anisotropy of the phenyl ring.

Similarly, H-3 in compound **11a** appears 0.8 ppm upfield as compared with that in compound **12a**, because of the deshielding effect of the C = O group. In this case, this effect can also be detected in protons H-1 and H-2 (values 2.6 - 2.3 in **11a**, and 1.5 - 1.6 in **12a**). A moderate upfield shift (0.4 ppm) of H-1p is now observed in derivative **11a**, which seems also produced by the anisotropy of the phenyl ring, more distant in this case than in compound **8a**.

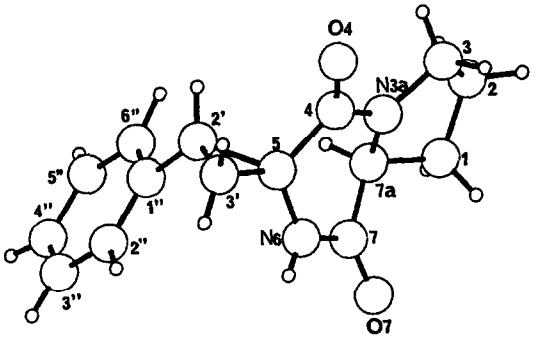


Figure 1. Molecular strucure[27] of compound **13** with the numbering system used in the crystallographic work

Those assignations were corroborated by X-ray studies on spiroderivative **13**. Table 1 gives the main geometrical characteristics of the molecule (Fig. 1 and 2). It may be noticed the different planarity around N3A and N6, where the angles around are 358.6(2) and 359.7(20)°, respectively. The packing, involving the two oxygen atoms in hydrogen interactions, seems to elongate the CO bonds, the angles NCC, opposite to the double bonds, being less than 120°.

Table 1. Selected geometrical parameters (A, °)

C1-C2	1.528 (5)	C1-C7A	1.514 (4)
C2-C3	1.528 (5)	C3-N3A	1.468 (4)
N3A-C4	1.333 (3)	N3A-C7A	1.468 (4)
C4-C5	1.501 (4)	C4-O4	1.236 (4)
C5-N6	1.433 (3)	C5-C2'	1.540 (4)
C5-C3'	1.486 (3)	N6-C7	1.347 (3)
C7-C7A	1.511 (4)	C7-O7	1.228 (4)
C2'-C3'	1.493 (4)	C2'-C1"	1.487 (4)
C2-C1-C7A	103.4 (3)	C1-C2-C3	105.5 (3)
C2-C3-N3A	103.5 (3)	C3-N3A-C7A	112.4 (2)
C3-N3A-C4	124.8 (3)	C4-N3A-C7A	121.4 (2)
N3A-C4-O4	123.5 (3)	N3A-C4-C5	112.9 (2)
C5-C4-O4	123.6 (2)	C4-C5-C3'	120.1 (3)
C4-C5-C2'	113.7 (3)	C4-C5-N6	114.7 (2)
C2'-C5-C3'	59.1 (2)	N6-C5-C3'	117.6 (3)
N6-C5-C2'	120.6 (2)	C5-N6-C7	121.4 (2)
C5-N6-H6	117 (3)	C7-N6-H6	122 (3)
N6-C7-O7	123.8 (2)	N6-C7-C7A	113.2 (2)
C7A-C7-O7	123.0 (2)	N3A-C7A-C7	109.3 (2)
C1-C7A-C7	115.7 (2)	C1-C7A-N3A	103.4 (2)
C5-C2'-C1"	121.6 (3)	C5-C2'-C3'	58.7 (2)
C3'-C2'-C1"	124.1 (3)	C5-C3'-C2'	62.3 (2)
C4-N3A-C7A-C7	-48.9 (3)	C7A-N3A-C4-C5	11.3 (4)
N3A-C4-C5-N6	31.2 (3)	C4-C5-N6-C7	-35.9 (3)
C5-N6-C7-C7A	-3.2 (3)	N6-C7-C7A-N3A	42.9 (3)
C2-C1-C7A-N3A	-32.4 (3)	C7A-C1-C2-C3	33.5 (3)
C1-C2-C3-N3A	-21.0 (3)	C2-C3-N3A-C7A	0.3 (3)
C3-N3A-C7A-C1	20.5 (3)	C2-C1-C7A-H7A	85 (2)
C2-C1-C7A-C7	-151.7 (3)	N3A-C4-C5-C2'	-113.2 (3)
N3A-C4-C5-C3'	180.0 (3)	C4-C5-C2'-C1"	134.5 (3)
N6-C5-C2'-C1"	-7.6 (4)	C5-C2'-C1"-C2"	76.9 (4)
C2'-C5-N6-C7	105.9 (3)	C3'-C2'-C1"-C2"	5.7 (5)
C1"-C2'-C3'-C5	109.2 (3)	C3'-C5-C2'-C1"	-113.4 (3)
C3'-C5-N6-C7	174.5 (3)	H2'-C2'-C3'-C5	-100 (2)
N6.....O4i	2.868 (3)	C3'.....O7ii	3.299 (4)
N6-H6	0.79 (4)	C3'-H3B'	0.94 (4)
H6.....O4i	2.08 (4)	H3B'.....O7ii	2.38 (4)
N6-H6	176 (4)	C3'-H3B'....O7ii	166 (3)
i = -x, 1/2y, -z		ii = -x, -1/2+y, -z	

The conformations of the fused 6,5-membered rings are, respectively, a distorted boat, more puckered around C7A, and quite a regular envelope, flapping at C1. Taking into account the internal conformation of the six-membered ring, the 3-membered ring comes out quite regularly: the angles between the planes formed by

C5, C2', C3' and N6, C5, C4 is 84.9(2) and the differences between the substituent torsion, N3A-C4-C5-C3'/C2', C7-N6-C5-C3'/C2' and the corresponding internal ones, N3A-C4-C5-N6, C7-N6-C5-C4, are around 146°. The phenyl ring conforms such that the torsion C2"-C1"-C2'-C3' is near zero (see Table 1).

The configuration of the molecule has been assesed from the chemical synthesis, which established an *S* character for the C7A atom. Then, C5 and C2' present an *R* character, as described by the configurational angles, ρ_1 +120° for the *R* configuration:

ρ_1(C7A) = τ(C2-C1-C7A-N3A) - τ(C2-C1-C7A-H7A) -117°

ρ_1(C5) = τ(C1"-C2'-C5-N6) - τ(C1"-C2'-C5-C3') +105°

ρ_1(2') = τ(C5-C3'-C2'-C5) - τ(C5-C3'-C2'-H2') +100°

This criterion is equivalent to the rotation sequence, but avoids the reference to any figure.[28]

The compound packs in the crystal as chains along the b axis (see Fig. 2), with two hydrogen interactions as shown in Table 1.

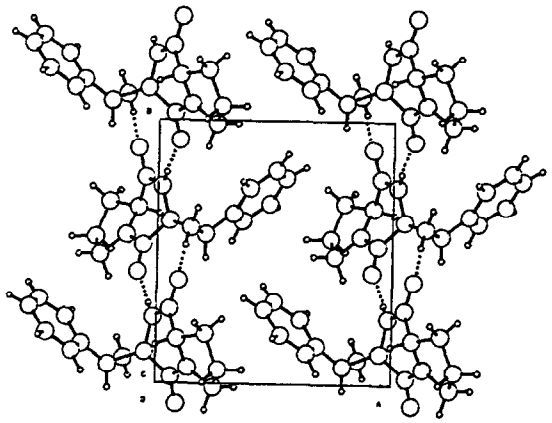


Figure 2. The crystal packing[27] of compound **13** as viewed down the c axis

Concluding remarks

Using N-methylephedrine or mandelic esters as chiral auxiliaries, we have obtained both enantiomers of *(Z)*-2-phenyl ACC. Although the d.e. of the cyclopropanation of the corresponding arylcinnamic esters was low, the resulting two diastereoisomers were easily separated by chromatography and/or recrystallization.

On the other hand, the high e.e. and yields obtained *via* diketopiperazines from *S*-proline and oxazolones makes this a good and quite general method to synthesize enantiomerically pure *(Z)*-2-alkyl(aryl) ACC.

EXPERIMENTAL SECTION

General methods. Melting points were taken using a Kofler hot-stage apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed on aluminium sheets precoated with silica gel (Merck, Kieselgel 60, F 254). Column chromatography separations were effected on silica gel (Merck, Kieselgel 60, 230-400 mesh) under pressure (flash chromatography). Infrared spectra were measured with a Perkin-Elmer 681 spectrometer for KBr pellets and are given in cm^{-1} units. ^{1}H-NMR spectra were recorded in $CDCl_3$ on a Varian XL-300 spectrometer, unless otherwise stated. ^{13}C-NMR spectra were recorded on a Bruker AM-200 (50 MHz). Chemical shifts are reported in δ units downfield from Me_4Si, and *J* values in Hz. Observed rotations at the Na-D line were obtained at 20 °C using a Perkin-Elmer 141 polarimeter. Photolysis were carried out in a Pyrex-cell with an Osram HQL-125 W lamp for solutions in dry benzene, under argon atmosphere.

(*R*)-1-Isopropoxycarbonylbenzyl 2-benzamidocinnamate (1a). A mixture of (*R*)-isopropyl mandelate (2.3 g, 12 mmol), (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (2.5 g, 10 mmol) and *p*-toluenesulfonic acid mohohydrate (0.2 g, 1 mmol) in tetrahydrofuran (50 ml) was refluxed for 24 h. The solvent was then removed in vacuo and the residue was dissolved in CH_2Cl_2 and neutralized with aqueous $NaHCO_3$. The organic layer was separated, washed with water and dried over sodium sulfate. After evaporation to dryness the residue was chromatographed (EtOAc-hexane 5:1) to yield 3.1 g (70%) of **1a** , as a solid, m.p. 109-111 °C; $[\alpha]_D$ = -58 (*c* = 0.67, $CHCl_3$); IR 3240, 1750, 1725, 1650; ^{1}H-NMR 1.10 and 1.20 (2 d, *J* = 6.0, 6H), *ca* 4.5 (m, 1H), 6.00 (s, 1H), *ca* 7.6 (m, 16H); ^{13}C-NMR 21.4, 21.6, 69.6, 75.7, 123.9, 127.4, 127.5, 128.6, 128.7, 129.1, 129.6, 129.9, 132.0, 133.5, 133.8, 133.9, 164.6, 165.8, 168.0; MS 249 (13), 107 (48), 105 (100), 79 (22), 77 (43).

(1*R*, 2*S*)-1-Phenyl-2-dimethylaminopropyl 2-benzamidocinnamate (1b). To a solution of (-)-N-methylephedrine (626 mg, 3.5 mmol) in dry THF (30 ml) at 10 °C under argon atmosphere, a catalytic amount of HNa (60% dispersion in mineral oil) was added. After 10 min at room temperature, (*Z*)-2-phenyl-4-benzylidene-5(4H)-oxazolone (884 mg, 3.5 mmol) was added. The mixture was stirred for 2 h, the solvent removed in vacuo and the residue chromatographed (CH_2Cl_2-MeOH, 98:2) to yield 1.4 g (91%) of **1b** as a white solid, mp = 64-65 °C, $[\alpha]_D$ = +95 (*c* = 1.1, $CHCl_3$); IR 3300, 1725, 1660, 1650; ^{1}H-NMR 1.13 (d, 3H, *J* = 6.1), 2.35 (s, 6H), *ca* 2.95 (m, 1H), 6.13 (d, 1H, *J* = 4.5), *ca* 7.6 (m, 15H); ^{13}C-NMR 9.37, 41.17, 63.69, 77.32, 124.4, 126.2, 127.2, 127.4, 128.1, 128.3, 128.5, 129.3, 129.6, 131.8, 132.5, 133.7, 133.8, 139.6, 164.32, 165,60. Anal. Calcd. for $C_{27}H_{28}N_2O_3$: C, 75.67; H, 6.59; N, 6.54. Found: C, 75.41; H, 6.65; N, 6.91.

Synthesis of the pyrazolines 2a and 3a. To an ethereal solution of diazomethane (1.26 g, 30 mmol) at 0 °C, compound **1a** (4.43 g, 10 mmol) was added portionwise. The mixture was kept for 5 days at this temperature, being monitored by TLC. Anhydrous $CaCl_2$ was added. The solution was filtered and evaporated to dryness in vacuo. The diastereomeric mixture **2a** + **3a** was chromatographed (benzene-ether, 6:1) to yield **2a** (2.3 g, 48 %) and **3a** (1.6 g, 33%).

(*R*)-1-Isopropoxycarbonylbenzyl (3*R*,4*R*)-3-benzamido-4-phenyl-1-pyrazoline-3-carboxylate (2a). White solid, mp = 125-126 °C; $[\alpha]_D$ = -129 (*c* = 0.8, $CHCl_3$); IR 3420, 1770, 1740, 1615; ^{1}H-NMR (C_6D_6) 0.88 and 0.96 (2 d, 6H, *J* = 6.2), 4.33 (dd, 1H, *J* = 7.8, *J* = 2.5), 4.87 (dd, 1H, *J* = 18.0, *J* = 7.8), 4.94 (m, 1H), 5.01 (dd, 1H, *J* = 18.0, *J* = 2.5), 6.21 (s, 1H), *ca* 7.1 (m, 15H).

(*R*)-1-Isopropoxycarbonylbenzyl (3*S*, 4*S*)-3-benzamido-4-phenyl-1-pyrazoline-3-carboxylate (3a). White crystals, mp = 133-134 °C; $[\alpha]_D$ = 0 (*c* = 0.9, $CHCl_3$); IR 3410, 1745, 1650; ^{1}H-NMR (C_6D_6) 0.86 and 1.01 (2 d, 6H, *J* = 6.2), 4.46 (dd, 1H, *J* = 4.0, *J* = 8.1), 4.96 (dd, 1H, *J* = 17.9, *J* = 8.1), *ca* 5.0 (m, 1H), 5.21 (dd, 1H, *J* = 17.9, *J* = 4.0), 6.20 (s, 1H), *ca* 7.09 (m, 15H).

General procedure for the synthesis of cyclopropyl compounds 4 and 5. A solution of the proper **2a**, **3a** or **2b/3b** (*ca* 1 mmol) in dry benzene (200 ml) was photolyzed under argon atmosphere until disappearance of the starting material (*ca* 6 h). The solvent was then removed in vacuo and the residue purified, either by crystallization (**4a**, **5a**) or by column chromatography (**2b/3b**) (3% MeOH : CH_2Cl_2).

(*R*)-1-Isopropoxycarbonylbenzyl (1*S*, 2*S*)-1-benzamido-2-phenylcyclopropanecarboxylate (4a). Obtained from **2a** (0.48 g, 1 mmol) as above, giving 0.36 g (80%), as a white solid, mp = 199-201 °C; $[\alpha]_D$ = -86 (*c* = 0.5, $CHCl_3$); IR 3350, 1760, 1740, 1655; ^{1}H-NMR 1.15 and 1.28 (2 d, 6H, *J* = 6.2), 1.97 (dd, 1H, *J* = 6.2, *J* = 8.2), 2.45 (dd, 1H, *J* = 9.4, *J* =6.2), 3.12 (dd, 1H, *J* = 9.4, *J* = 8.2), 5.06 (m, 1H), 5.96 (s, 1H), 6.08 (s, broad, 1H), *ca* 7.3 (m, 15H); ^{13}C-NMR 21.1, 21.4, 21.7, 33.1, 39.1, 69.6, 75.3, 126.9, 127.4, 127.7, 128.5, 128.6, 128.7, 128.8, 129.1, 131.7, 133.7, 134.1, 134.2, 168.1, 168.4, 170.9; MS 280 (19), 105 (100), 77 (28).

(*R*)-1-Isopropoxycarbonylbenzyl (1*R*, 2*R*)-1-benzamido2-phenylcyclopropanecarboxylate (5a). From compound **3a** (0.48 g, 1 mmol) we obtained 0.36 g, (80%) of a white solid, mp = 143-146 °C; $[\alpha]_D$ = -13 (*c* = 0.5, $CHCl_3$) IR 3340, 1735, 1650; ^{1}H-NMR 1.14 and 1.27 (2 d, 6H, *J* = 6.3), 1.95 (dd, 1H, *J* = 6.4, *J* = 8.1), 2.43 (dd, 1H, *J* = 9.6, *J* = 6.4), 3.34 (dd, 1H, *J* = 9.6, *J* = 8.1), 5.05 (m, 1H), 5.94 (s, 1H), 6.04 (s, broad, 1H), *ca* 7.4 (m, 15H); MS 280 (20), 136 (8), 105 (100), 77 (23).

Photolytic products of the crude mixture of pyrazolines **2b** + **3b** as above were chromatographed (3% MeOH-CH_2Cl_2) to give **4b** + **5b**.

(1*R*, 2*S*)-1-Phenyl-2-dimethylaminopropyl (1*S*, 2*S*)-1-benzamido-2-phenylcyclopropane carboxylate (4b). Yield: 197 mg (38%). White solid, mp = 119-122 (dec); $[\alpha]_D$ = -12.5 (*c* = 4.3, $CHCl_3$); IR 3320, 1720, 1650; ^{1}H-NMR 0.98 (d, 3H, *J* = 6.7), 1.89 (dd, 1H, *J* = 6.0, *J* = 8.1), 2.30 (dd, 1H, *J* = 6.0, *J* = 7.6), 2.32 (s, 6H), 2.83 (dq, 1H, *J* = 6.7, *J* = 4.2), 3.08 (dd, 1H, *J* = 8.1, *J* = 7.6), 6.00 (d, 1H, *J* = 4.2), *ca* 7.3 (m, 10H); Anal. Calcd. for $C_{28}H_{30}N_2O_3$: C, 75.99; H, 6.83; N, 6.33. Found: C, 75.80; H, 7.10; N, 6.36.

(1*R*, 2*S*)-1-Phenyl-2-dimethylaminopropyl (1*R*, 2*R*)-1-benzamido-2-phenylcyclopropane carboxylate (5b). Yield: 98 mg (19%). Syrup, with slight impurities which could not been removed. IR 3300, 1710, 1608; ^{1}H-NMR 1.01 (d, 3H, *J* = 6.8), 1.88 (dd, 1H, *J* = 6.0, *J* = 8.1), 2.29 (s, 6H), 2.30 (dd, 1H, *J* = 6.0, *J* = 9.4), *ca* 2.8 (m, 1H), 3.05 (dd, 1H, *J* = 8.1, *J* = 9.4), 5.99 (d, 3H, *J* = 4.8), *ca* 7.3 (m, 15H); MS m/e 72 (100), 77 (9), 105 (14), 162 (13), 442 (1).

(1*S*, 2*S*)-1-Amino-2-phenylcyclopropanecarboxylic acid [(1*S*, 2*S*)-6]. To a solution of **4a** (1.4 g, 3.0 mmol) in HOAc (20 ml), 6N HCl (10 ml) was added, and the mixture was refluxed for 6 h. The cooled solution was extracted with EtOAc (3 x 20 ml) and the aqueous phase was treated with active charcoal and evaporated to dryness. The crude product (0.6 g, 70%) was recrystallized from EtOH/Et_2O, mp =200-205 °C (dec); $[\alpha]_D$ = -102 (*c* = 0.6, H_2O); IR 3500-2400, 1735; ^{1}H-NMR (D_2O) 1.67 (dd, 1H, *J* = 8.5, *J* = 6.8), 1.81 (dd, *J* = 9.8, *J* = 6.8), 3.04 (dd, 1H, *J* = 9.8, *J* = 8.5), 7.25 (m, 5H).

Similarly, **4b** (92 mg, 0.2 mmol) was treated with dioxane (3 ml) and 6N HCl (3 ml) at 100 °C for 17 h. The solution was cooled, diluted with H_2O and extracted with CH_2Cl_2 (3 x 25 ml). The aqueous phase was adjusted first to pH=10 (10% NaOH), extracted again with CH_2Cl_2 (4 x 25 ml) and then led to pH = 1 (12 N HCl) and the solvent was removed in vacuo. The residual solid was extracted twice with boiling absolute EtOH and the solvent evaporated in vacuo to give 28 mg (65 %) of *(1S,2S)*-**6**, as a solid identical to that obtained from **4a**.

(1*R*, 2*R*)-1-Amino-2-phenylcyclopropanecarboxylic acid. [(1*R*, 2*R*)-6]. Compound **5a** (0.9 g, 2.0 mmol) was refluxed with HOAc and 6N HCl, as described for **4a** (see above), to give 0.3 g (70%) of *(1R, 2R)*-**6**, as a solid, mp = 197-200 °C (dec). $[\alpha]_D$ = +100 (*c* = 0.7, H_2O).

Synthesis of spiropyrazolines 8a,b and 9a,b. General Procedure. To a solution of diazomethane (*ca* 1 g, 30 mmol) in benzene (25 ml), compound **7a** or **7b**[21] (10 mmol) was added portionwise. The mixture was stirred to completion of reaction (3-5 days). Occasional new additions of diazomethane were necessary to complete the reaction. Residual diazomethane was eliminated by addition of anhydrous $CaCl_2$. Filtration and evaporation to dryness gave a mixture of two pyrazolines in each case, **8a** + **9a**, or **8b** + **9b**, respectively. The diastereomeric ratio (95:5) was determined by ^{1}H-NMR on the crude mixtures. Crystallization from EtOAc gave compounds **8a** or **8b**.

6-Acetyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'*S*, 4'*S*)-4'-phenyl-1'-pyrazoline] (8a). Yield 2.3 g (70%) mp = 171-173 °C; $[\alpha]_D$ = -266 (*c* = 1.6, $CHCl_3$); IR 1730, 1710, 1685, 1675; ^{1}H-NMR *ca* 2.0 (m, 3H), 2.30 (s, 3H), *ca* 2.3 (m, 1H), 3.66 (dd, 1H, *J* = 9.0, *J* = 8.0), *ca* 3.7 (m, 2H), *ca* 3.8 (m, 1H), 5.10 (dd, 1H, *J* =18.1, *J* = 8.0), 5.28 (dd, 1H, *J* = 18.1, *J* = 9.0), *ca* 7.2 (m, 5H); ^{13}C-NMR 22.0, 28.0, 29.6, 46.1, 58.6, 84.3, 104.9, 128.4, 128.9, 129.0, 133.5, 162.9, 168.4, 173.6. Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.58; H, 5.52; N, 17.18. Found: C, 62.72; H, 5.57; N, 17.20.

6-Benzoyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'*S*, 4'*S*)-4'-phenyl-1'-pyrazoline] (8b). Yield 0.72 g (70%) mp = 194-196 °C; $[\alpha]_D$ = -260 (*c* = 0.56, $CHCl_3$); IR 1710, 1675; ^{1}H-NMR 1.92 (m, 2H), 2.16 (m, 2H), 3.40 (dd, 1H, *J* = 9.0, *J* = 8.8), *ca* 3.7 (m, 1H), 3.70 (m, 1H), 3.95 (m, 1H), 5.08 (dd, 1H, *J* = 18.1, *J* = 9.0), 5.37 (dd, 1H, *J* = 18.1, *J* = 8.8), *ca* 7.5 (m, 10 H); ^{13}C-NMR 22.2, 29.8, 45.9, 46.8, 58.5, 84.8, 104.5, 128.6, 128.7, 129.0, 129.2, 129.4, 132.8, 133.5, 134.3, 163.6, 168.6, 172.4; Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.04; H, 5.15; N, 14.43. Found: C, 68.27; H, 5.04; N, 14.30.

By chromatography of the mother liquors of **8a** and **8b** (EtOAc-hexane 1:1), the minor diastereoisomers **9a** and **9b** were obtained.

6-Acetyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'*R*, 4'*R*)-4'-phenyl-1'-pyrazoline] (9a). Yield: 0.06 g (2%). White solid, mp = 137-139 °C, $[\alpha]_D$ = +16 (*c* = 0.8, $CHCl_3$); IR 1735, 1720, 1710, 1680; ^{1}H-NMR 1.56 (s, 3H), *ca* 2.2 (m, 3H), *ca* 2.6 (m, 1H), *ca* 3.9 (m, 2H), 4.90 (m, 1H), 4.95 (dd, 1H, *J* = 9.1, *J* = 9.0), 5.20 (dd, 1H, *J* = 18.1, *J* = 9.1), 5.25 (dd, 1H, *J* = 18.1, *J* = 9.0), *ca* 7.1 (m, 5H); ^{13}C-NMR 22.4, 27.7, 28.9, 38.5, 47.0, 59.4, 81.0, 107.5 , 127.0, 128.4, 128.8, 133.7, 160.6, 169.9, 177.2; Anal. Calcd for $C_{17}H_{18}N_4O_3$: C, 62.58; H, 5.52; N, 17.18. Found: C, 62.76; H, 5.42; N, 6.92.

6-Benzoyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'*R*, 4'*R*)-4'-phenyl-1'-pyrazoline] (9b). Yield: 0.6 g (2%). White solid, mp = 177-178 °C; $[\alpha]_D$ = +2 (*c* = 1.0, $CHCl_3$); IR 1720, 1705, 1670; ^{1}H-NMR *ca* 2.2 (m, 3H), *ca* 2.5 (m, 1H), *ca* 3.8 (m, 1H), *ca* 4.0 (m, 1H), 4.97 (dd, 1H, *J* = 9.4, *J* = 9.0), 5.04 (m, 1H), 5.20 (dd, 1H, *J* = 18.1, *J* = 9.0), 5.32 (dd, 1H, *J* = 18.1, *J* = 9.4), *ca* 7.0 (m, 10H); Anal. Calcd. for $C_{22}H_{20}N_4O_3$: C, 68.04; H, 5.15; N, 14.43. Found: C, 67.90; H, 5.20; N, 14.64.

6-Acetyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*R*, 2'*R*)-2'-phenyl cyclopropane] (11a). A solution of **8a** (3.3 g, 10 mmol) in dry benzene (300 ml) was photolyzed for 7 h under argon atmosphere. The solvent was removed in vacuo and the residue chromatographed (EtOAc-hexane 1:1) to give 2.7 g (90%) of **11a**, as a white solid, mp = 144-146 °C; $[\alpha]_D$ = -270 (*c* = 1.1, $CHCl_3$); IR 1720, 1680; ^{1}H-NMR *ca* 2.0 (m, 2H), *ca* 2.2 (m, 2H), 2.31 (dd, 1H, *J* = 7.8, *J* = 7.4), 2.33 (s, 3H), 2.60 (dd, 1H,

J = 10.0, *J* = 7.4), 2.66 (dd, 1H, *J* = 10.0, *J* = 7.8), *ca* 3.6 (m, 2H), 4.11 (dd, 1H, *J* = 7.9, *J* = 7.7), *ca* 7.2 (m, 5H); ^{13}C-NMR 15.6, 23.5, 27.4, 27.5, 32.7, 44.9, 46.8, 60.5, 127.4, 127.5, 128.7, 134.3, 166.2, 172.0. Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.46; H, 6.04; N, 9.40. Found: C, 68.77; H, 6.06; N, 9.11.

6-Acetyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*S*, 2'*S*)-2'-phenyl cyclopropane] (12a). Obtained by photolysis of compound **9a** (0.33 g, 1 mmol). Yield: 0.27 g (90%). White solid, mp = 177-179 °C; $[\alpha]_D$ = -44 (*c* = 0.5, $CHCl_3$); IR 1740, 1720, 1675; ^{1}H-NMR 1.54 (dd, 1H, *J* = 10.0, *J* = 5.4), 1.62 (dd, 1H, *J* = 7.9, *J* = 5.4), *ca* 2.0 (m, 2H), 2.01 (s, 3H), *ca* 2.3 (m, 2H), 3.49 (dd, 1H, *J* = 10.0, *J* = 7.9), *ca* 3.6 (m, 2H), 4.51 (m, 1H), *ca* 7.2 (m, 5H), ^{13}C-NMR 19.9, 23.7, 26.0, 26.7, 27.3, 44.6, 46.6, 61.3, 127.0, 127.5, 128.1, 135.2, 166.5, 171.0, 173.7; Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.46; H, 6.04; N, 9.40. Found: C, 68.70; H, 6.02; N, 9.30.

6-Benzoyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*R*, 2'*R*)-2'-phenyl cyclopropane] (11b). Photolysis of **8b**, under similar conditions to those used for **8a** led to extensive decomposition of **8b** into a mixture of compounds, from which **11b** was isolated in 25% yield, as a white solid, mp = 161-162 °C; $[\alpha]_D$ = -321 (c = 0.62, $CHCl_3$); IR 1735, 1700, 1680; ^{1}H-NMR 1.94 (dd, 1H, *J* = 7.9, *J* = 8.0), *ca* 2.0 (m, 2H), *ca* 2.3 (m, 2H), 2.70 (dd, 1H, *J* = 8.0, *J* = 9.8), 2.83 (dd, 1H, *J* = 7.9, *J* = 9.8), *ca* 3.6 (m, 2H), 4.37 (t, 1H, *J* = 7.6), *ca* 7.3 (m, 10H); ^{13}C-NMR 14.7, 23.5, 26.8, 34.4, 45.3, 47.6, 59.7, 127.9, 128.9, 129.1, 130.0, 133.1, 134.1, 134.2, 166.1, 170.1, 171.5; Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.33; H, 5.55; N, 7.78. Found: C, 73.56; H, 5.52; N, 7.57.

Pyrolysis of compound 9b. Compound **9b** (0.39 g, 1.0 mmol) was refluxed in dry toluene (10 ml) for 12 h. The solvent was then removed in vacuo and the residual syrup was chromatographed (EtOAc:hexane 1:1) to give compounds **10** and **12b**.

6-Benzoyl-(*Z*)-5-(1-phenylethylidene)-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione (10). Yield: 0.09 g (25%). White solid, mp = 202-204 °C; $[\alpha]_D$ = +23 (*c* = 0.9, $CHCl_3$); IR 1740, 1695, 1660; ^{1}H-NMR *ca* 2.0 (m, 2H), 2.35 (s, 3H), *ca* 2.4 (m, 2H), *ca* 3.7 (m, 2H), 4.39 (t, 1H, *J* =7.5), *ca* 7.1 (m, 10 H,); ^{13}C-NMR 21.2, 23.6, 23.7, 26.5, 45.3, 60.0, 127.6, 128.0, 128.2, 128.4, 128.5, 129.3, 132.5, 133.6, 139.0, 142.4, 161.6, 167.9, 169.0; Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.33; H, 5.55; N, 7.78. Found: C, 73.6; H, 5.40; N, 7.61.

6-Benzoyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*S*, 2'*S*)-2'-phenyl cyclopropane] (12b).- Yield: 0.18 g (25%), as a white solid, mp = 153-156 °C; $[\alpha]_D$ = -90 (*c* = 0.9, $CHCl_3$); IR 1750, 1690, 1680; ^{1}H-NMR 1.63 (dd, 1H, *J* = 9.8, *J* = 8.2), 1.88 (dd, 1H, *J* = 8.2, *J* = 5.2), *ca* 2.0 (m, 2H), *ca* 2.3 (m, 2H), 3.57 (dd, 1H, *J* = 9.8, *J* = 8.2), 3.61 (m, 2H), 4.55 (t, 1H, *J* = 7.7), *ca* 7.2 (m, 10H); ^{13}C-NMR 19.4, 23.8, 26.4 26.6, 45.1, 48.3, 60.3, 127.0, 127.8, 128.9, 130.5, 132.9, 133.2, 166.8, 170.7, 172.1; Anal. Calcd. for $C_{22}H_{20}N_2O_3$: C, 73.33; H, 5.55; N, 7.78. Found: C, 73.30; H, 5.67; N, 7.64.

***(1R, 2R)*-1-Amino-2-phenylcyclopropanecarboxylic acid [*(1R, 2R)-6*].** To a solution of **11a** (0.9 g, 3.0 mmol) in HOAc (5 ml), 6N HCl (5 ml) was added and the mixture was refluxed for 24 h. The cool solution was diluted, extracted with $CHCl_3$ (2 x 10 ml) the aqueous layer treated with active charcoal, filtered and evaporated to dryness. The residue was dissolved in water (5 ml) and solid K_2CO_3 was added to pH = 8 to precipitate *(1R, 2R)*-**6** (0.4 g, 75%), together with small amounts of stiryl glycine.[22] Elimination of the solvent and recrystallization from absolute EtOH/Et_2O yielded an analytical sample, mp = 201-205 °C (dec); $[\alpha]_D$ = +105 (*c* = 0.7, H_2O); ^{1}H-NMR (D_2O) (see above).

(7a*S*)-3a,6-Diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*R*, 2'*R*)-2'-phenylcyclopropane] (13). To a solution of compound **11a** (3.0 g, 0.01 mol) in dioxane (50 ml), 2N HCl (50 ml, 0.1 mol) was added, and the mixture was heated at 60 °C for 3 h. By cooling and concentration in vacuo a solid was obtained, which was recrystallized (MeOH), giving 1.8 g (70%) of **13**, as white crystals, mp = 292-293 °C; $[\alpha]_D$ = +100 (*c* = 0.6, $CHCl_3$); IR 3210, 1690, 1650; ^{1}H-NMR 1.40 (dd, 1H, *J* = 7.7, *J* = 6.5), *ca* 2.0 (m, 3H), 2.29 (dd, 1H, *J* = 9.8, *J* = 6.5), *ca* 2.3 (m, 1H), 2.74 (dd, 1H, *J* = 9.8, *J* = 7.7), *ca* 3.6 (m, 2H), 4.09 (dd, 1H, *J* = 9.1, *J* = 7.0), 5.70 (s, 1H), *ca* 7.2 (m, 5H); Anal. Calcd. for $C_{15}H_{16}N_2O_2$: C, 70.31; H, 6.25; N, 10.94. Found: C, 69.97; H, 6.43; N, 10.82.

Synthesis of N-*tert*-butoxycarbonyl-diketopiperazines 16. General procedure Triethylamine (1.01 g, 10.3 mmol), 4-dimethylaminopyridine (1.30 g, 10.3 mmol) and di-*t*-butyl dicarbonate (4.50 g, 20.6 mmol) were added to a solution of the corresponding diketopiperazine **15**[21] (10.3 mmol) in dry dichloromethane under argon. The mixture was stirred overnight at r.t. under argon and then evaporated. The raw product **16** was purified by filtration through silica gel (eluent: hexane/ethyl acetate 1:1).

6-*tert*-Butoxycarbonyl-(Z)-5-ethylidene-(7aS)-3a,6-diazaperhydroindane-4,7-dione (16b). Yield: 2.0 g (70%). mp = 77-79 °C; $[\alpha]_D$ = -60 (*c* = 1.32, $CHCl_3$). ^{1}H-NMR 6.39 (c, 1H, *J* = 7.5), 4.00 (t, 1H, *J* = 8.0), 3.53 (m, 2H), 2.24 (m, 2H), 2.0-1.8 (m, 2H), 1.69 (d, 3H, *J* = 7.5), 1.51 (s, 9H). ^{13}C-NMR 166.6, 161.4, 148.9, 131.0, 125.9, 84.8 59.9, 44.8, 27.6, 27.2, 23.0, 13.5. IR 1745, 1680, 1660, 1650.

Anal. Calcd. for $C_{14}H_{20}N_2O_4$: C, 59.98; H, 7.19; N, 9.99. Found: C, 60.05; H, 7.43; N, 9.79.

6-*tert*-Butoxycarbonyl-(Z)-5-propylidene-(7aS)-3a,6-diazaperhydroindane-4,7-dione (16c). Yield: 2.25 g (75%). White solid, mp = 93-94 °C; $[\alpha]_D$ = -6 (*c* = 1.53, $CHCl_3$). ^{1}H-NMR 6.23 (dd, 1H, *J* = 6.9, *J* = 8.1), 4.01 (t, 1H, *J* = 8.1), 3.53 (m, 2H), 2.35 (m, 2H), 2.1-1.8 (m, 4H), 1.45 (s, 9H), 1.01 (t, 3H, *J* = 7.5). ^{13}C-NMR (C_6D_6) 166.7, 161.6, 151.1, 131.8, 130.9, 84.9, 59.7, 45.5 , 28.3, 28.3, 23.2, 22.1, 13.3. IR 1780, 1750, 1680, 1650. Anal. Calcd. for $C_{15}H_{22}N_2O_4$: C, 61.21 H, 7.53; N, 9.52. Found: C, 60.99; H, 7.60; N, 8.99.

6-*tert*-Butoxycarbonyl-(Z)-5-isobutylidene-(7aS)-3a,6-diazaperhydroindane-4,7-dione (16d). Yield: 1.8 g (57%). White solid, mp = 123-125 °C; $[\alpha]_D$ = -3 (*c* = 2.4, $CHCl_3$). ^{1}H-NMR 6.09 (d, 1H, *J* = 11.0), 4.02 (t, 1H, *J* = 7.9), 3.54 (m, 2H), 2.4-1.8 (m, 5H), 1.53 (s, 9H), 1.05 (d, 3H, *J* = 6.5), 0.98 (t, 3H, *J* = 6.5). ^{13}C-NMR 166.4, 161.7, 149.9, 137.3, 127.8, 85.0, 59.5, 44.9, 27.6, 27.1, 23.0, 22.6, 20.0. IR 1760, 1750, 1740, 1715. Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.31; H, 7.85; N, 9.09. Found: C, 62.18; H, 7.88; N, 9.26.

Synthesis of pyrazolines 17. General procedure. A benzene solution of diazomethane was added dropwise to a stirred solution of N-*tert*-butoxicarbonyl derivatives **16** (4.2 mmol) in benzene. The solution was stirred for 7 days at r.t. and treated with anhydrous calcium chloride to destroy excess of diazomethane. After removal of the solvent, a few ml of ether were added. Compounds **17**, which deposited on cooling, were collected by filtration and recrystallized from hexane/ethyl acetate.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'S, 4'S)-4'-methyl-1'-pyrazoline] (17b). Yield: 1.2 g (86 %). White solid, mp = 115-118 °C; $[\alpha]_D$ = 0 (*c* = 1.15, $CHCl_3$). ^{1}H-NMR 4.82 (dd, 1H, *J* = 8.7, *J* = 18.2), 4.45 (dd, 1H, *J* = 4.9, *J* = 18.2), 4.10 (dd, 1H, *J* = 6.8, *J* = 9.5), 3.6-3.4 (m, 2H), 2.5-1.8 (m, 5H), 1.42 (s, 9H), 1.08 (d, 3H, *J* = 7.2). ^{13}C-NMR 166.7, 162.4, 149.6, 104.6, 85.8, 85.6, 58.6, 33.3, 29.0, 27.5, 22.4, 14.5. IR 1780, 1755, 1710, 1675. Anal. Calcd. for $C_{15}H_{22}N_4O_4$: C, 55.88; H, 6.88; N, 17.38. Found: C, 55.77; H, 6.84; N, 17.31.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'S, 4'S)-4'-ethyl-1'-pyrazoline] (17c). Yield: 1.3 g (95%). White solid, mp = 138 °C; $[\alpha]_D$ = -7 (*c* = 0.76, $CHCl_3$). ^{1}H-NMR 4.78 (dd, 1H, *J* = 8.6, *J* = 18.2), 4.50 (dd, 1H, *J* = 5.1, *J* = 18.2), 4.12 (dd, 1H, *J* = 6.6, *J* = 9.1), 3.61 and 3.51 (2m, 2H), 2.5-1.8 (m, 5H), 1.44 (m, 2H), 1.40 (s, 9H), 0.88 (t, 3H, *J* = 7.3). ^{13}C-NMR (C_6D_6) 167.0, 162.2, 151.5, 105.0, 85.0, 84.0, 58.6, 45.4, 41.3, 29.6, 29.1, 22.8, 21.9, 13.1. IR 1780, 1750, 1720, 1680. Anal. Calcd. for $C_{16}H_{24}N_4O_4$: C, 57.08; H, 7.19; N, 16.71. Found: C, 57.07; H, 7.10; N, 16.50.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-3'-[(3'S, 4'S)-4'-*iso*-propyl-1'-pyrazoline] (17d). Yield: 0.9 g (64%). White solid, mp = 135-138 °C; $[\alpha]_D$ = +19° (*c* = 1.1, $CHCl_3$). ^{1}H-NMR 4.84 (dd, 1H, *J* = 8.9, *J* = 18.3), 4.52 (dd, 1H, *J* = 7.2, *J* = 18.3), 4.15 (dd, 1H, *J* = 6.1, *J* = 9.8), 3.9-3.5 (m, 2H), 2.48, 2.11 and 1.89 (3m, 6H), 1.40 (s, 9H), 0.91 (d, 3H, *J* = 6.4), 0.60 (t, 3H, *J* = 6.6).^{13}C-NMR 169.3, 160.5, 152.1, 103.4, 85.7, 83.1, 59.1, 46.6, 41.6, 29.1, 27.4, 26.3, 23.5, 22.3, 21.9. IR 1760, 1705, 1680. Anal. Calcd. for $C_{17}H_{26}N_4O_4$: C, 58.28; H, 7.48; N, 15.99. Found: C, 57.98; H, 7.46; N, 15.78.

General procedure for the synthesis of spirocyclopropanes 18. A solution of the corresponding pyrazoline **17** (3 mmol) in dry benzene (300 ml) was irradiated under argon using an Osram HQL-125W lamp for 6-8 h. The solvent was evaporated and the residue recrystallized from ethyl acetate/hexane.

6-*tert*-Butoxycarbonyl-(7a*S*)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'*R*, 2'*R*)-2'-phenylcyclopropane (18a). Yield: 1.02 g, (95%). White solid, mp =167-169 °C (dec) (EtOAc); $[\alpha]_D$ = -160 (*c* = 1.0, $CHCl_3$); IR 1740, 1735, 1695; ^{1}H-NMR (C_6D_6) *ca* 1.1 (m, 2H), 1.33 (s, 9H), *ca* 1.5 (m, 1H), *ca* 1.9 (m, 1H), 2.24 (dd, 1H, *J* = 7.6, *J* = 7.3), 2.37 (dd, 1H, *J* = 9.8, *J* = 7.6), 2.77 (dd, 1H, *J* = 9.8, *J* = 7.3), *ca* 3.0 (m, 1H), *ca* 3.15 (m, 1H), 3.74 (t, 1H, *J* = 7.8), *ca* 7.0 (m, 5H); ^{13}C-NMR 15.6, 23.5, 27.1, 27.8, 32.7, 45.0, 47.6, 60.2, 84.2, 127.5, 127.7, 128.6, 134.0, 150.6, 166.3, 169.5; Anal. Calcd. for $C_{20}H_{24}N_2O_4$: C, 67.42; H, 6.74; N, 7.86. Found: C, 67.3; H, 6.61; N, 7.98.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'S, 2'S)-2'-methylcyclopropane] (18b). Yield: 0.75 g (82%). Colourless syrup. ^{1}H-NMR 4.12 (t, 1H, *J* = 7.8), 3.48 (m, 2H), 2.29 (m, 2H), 2.10 (dd, 1H, *J* = 7.0, *J* = 9.3), 1.93 (m, 3H), 1.49 (s, 9H), 1.28 (m, 1H), 1.12 (d, 3H, *J* = 6.0), 1.06 (t, 1H, *J* = 7.0). ^{13}C-NMR 170.3, 166.8, 150.5, 84.5, 60.0, 44.9, 27.8, 27.0, 23.5, 21.8, 17.3, 13.2.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'S, 2'S)-2'-ethylcyclopropane] (18c). Yield: 0.93 g (99%). White solid, mp = 138 °C; $[\alpha]_D$ = -7 (*c* = 0.6, $CHCl_3$). ^{1}H-NMR 4.12 (t, 1H, *J* = 7.9), 3.46 (m, 2H), 2.25 (m, 2H), 2.1-1.8 (m, 3H), 1.45 (s, 9H), 1.40 and 1.21 (2m, 2H), 1.18 (m, 1H), 1.04 (t, 1H, *J* = 6.8), 0.95 (t, 3H, *J* = 7.2). ^{13}C-NMR (C_6D_6) 170.0, 166.1, 151.7, 83.9, 59.8, 45.0, 29.2, 28.4, 27.7, 27.4, 23.2, 21.6, 15.8, 13.5. IR 1740, 1680, 1670. Anal. Calcd. for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.85; N, 9.08. Found: C, 62.54; H, 7.80; N, 9.14.

6-*tert*-Butoxycarbonyl-(7aS)-3a,6-diazaperhydroindane-4,7-dione-5-spiro-1'-[(1'S, 2'S)-2'-*iso*-propylcyclopropane] (18d). Yield: 0.82 g (90%). White solid, mp = 148-150 °C; $[\alpha]_D$ = +1 (*c* = 1.21, $CHCl_3$). ^{1}H-NMR 4.32 (t, 1H, *J* = 7.8), 3.50 (m, 2H), 2.31 (m, 2H), 2.1 -1.9 (m, 3H),1.52 (s, 9H), 1.47 (m, 1H), 1.15 (d, 3H, *J* = 6.5), 1.13 (dd, 1H, *J* = 4.5, *J* = 10.3), 0.98 (d, 3H, *J* = 6.8), 0.88 (dd, 1H, *J* = 4.5, *J* = 8.5). ^{13}C-NMR 171.6, 167.0, 151.4, 84.6, 60.3, 46.5, 44.8, 30.2, 27.7, 26.9, 26.2, 23.5,22.7, 23.6, 19.0. IR 1750, 1735, 1680. Anal. Calcd. for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69. Found: C, 62.98; H, 8.28; N, 8.56.

Synthesis of cyclopropane amino acids 6b-d. General procedure. A solution of the proper spirocyclopropane-derivative **18** (1.8 mmol) in 12 ml of concentrated hydrochloric acid/ acetic acid (3:1) was refluxed for 24 h. The reaction mixture was washed with dichloromethane. The aqueous phase was treated with charcoal, filtered, evaporated *in vacuo* and loaded on an ion-exchange colum (Amberlite CG-120, Na^+ form). Amino acids **6b-d** and *S*-proline were eluted from the column with 0.2M ammonium formate at different pH. The ninhydrin-positive fractions of each amino acid were combined and lyophilized.

***(1S, 2R)*-1-Amino-2-methyl-1-cyclopropanecarboxylic acid (6b).** *S*-Proline was eluted with 0.2M ammonium formate at pH = 2.9 and **6b** at pH = 4.3. Yield: 138 mg (69%). mp = 217-219 °C (dec); $[\alpha]_D$ = +70 (*c* = 0.7, H_2O) [lit.[26] +73.5 (*c* = 0.4, H_2O)]. ^{1}H-NMR (D_2O) 1.79 (m, 1H), 1.60 (dd, 1H, *J* = 6.2, *J* = 9.9), 1.15 (d, 3H, *J* = 6.5), 1.03 (dd, 1H, *J* = 6.2, *J* = 8.0). ^{13}C-NMR (D_2O) 147.6, 39.4, 21.6, 21.4, 12.4. IR 3600-2800, 1730.

***(1S, 2R)*-1-Amino-2-ethyl-1-cyclopropanecarboxylic acid (6c)** *S*-Proline was eluted with 0.2M ammonium formate at pH = 3.4 and amino acid **6c** at pH = 4.5. Yield: 210 mg (76%), mp = 182-183 °C (lit.[26] 183 °C); $[\alpha]_D$ = +64 (*c* = 1.1, H_2O) [lit.[26] +65 (*c* = 1.83, H_2O)]. ^{1}H-NMR (D_2O) 1.83 (m, 1H), 1.69 (dd, 1H, *J* = 6.1, *J* = 9.9), 1.60 (m, 1H), 1.44 (m, 1H), 1.15 (dd, 1H, *J* = 6.1, *J* = 8.0), 1.06 (t, 3H, *J* = 7.3). ^{13}C-NMR (D_2O) 174.5, 28.8, 21.5, 20.3, 13.8. IR 3570-2500, 1730.

***(1S, 2R)*-1-Amino-2-*iso*-propyl-1-cyclopropanecarboxylic acid (6d).** With 0.2M ammonium formate at pH = 3.2 was eluted *S*-proline and at pH = 4.1 compound **6d**. Yield: 180 mg (55%), mp = 221-224 (dec); $[\alpha]_D$ = +36 (*c* = 0.59, H_2O). ^{1}H-NMR (D_2O) 1.47 (m, 2H), 1.15 (m, 1H), 0.96 (m, 1H), 0.90 (d, 3H, *J* = 6.5), 0.83 (d, 3H, *J* = 6.5). ^{13}C-NMR (D_2O) 174.3, 35.0, 28.8, 22.8, 22.5, 19.9. IR 3550-2700, 1730.

(7a*S*)-3a,6-Diaza-7-ethoxy-3a,4,5,7a-tetrahydroindane-4-one-5-spiro-1'-[(1'*R*, 2'*R*)-2'-phenylcyclopropane (19). To a suspension of compound **13** (2.56 g, 10 mmol) in CH_2Cl_2 (25 ml), F_4BOEt_3 (3.8 g, 20 mmol) was added. The mixture was stirred for 24 h under argon atmosphere and poured on a cold (0 °C) phosphate buffer 2.2 M solution (pH = 7). The aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml), the organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo to give a syrup which was chromatographed (EtOAc : Hexane 1: 1). Compound **19** (2.56 g, 90%) was obtained as a solid, mp = 98 °C (EtOAc). IR 1680, 1640; ^{1}H-NMR 1.05 (t, 3H, *J* = 7.1), 1.58 (dd, 1H, *J* = 7.8, *J* = 4.6),*ca* 1.9 (m, 3 H), *ca* 2.2 (m, 1H), 2.29 (dd, 1H, *J* = 9.6, *J* = 4.6), 2.76 (dd, 1H, *J* = 9.6, *J* =7.8), *ca* 3.4 (m, 1H), *ca* 3.8 (m, 1H), 3.86 and 3.94 (2m, 2H), 3.98 (dd, 1H, *J* = 14.2, *J* = 7.1). Anal. Calcd. for $C_{17}H_{20}N_2O_2$: C,71.83; H, 7.04; N, 9.86. Found: C, 72.10; H, 7.30; N, 9.85.

***N*-[(*1R, 2R*)-1-*tert*-Butoxycarbonylamino-2-phenylcyclopropyl-1-carbonyl]-(*S*)-proline (20).** To a solution of compound **18a** (3.6 g, 0.01 mol), in THF (100 ml), 1N NaOH (30 ml, 0.03 mol) was added. The mixture was stirred for 1 h, acidified (10% HCl), and extracted with CH_2Cl_2 (3 x 50 ml). The solution was dried with Na_2SO_4 and the solvent removed in vacuo, and the residue (3.4 g, 90 %) recrystallized (EtOAc-hexane) to give **20** as a white solid, mp = 180-183 °C; $[\alpha]_D$ = -10 (*c* = 0.4, $CHCl_3$); IR 3540-3160, 1730, 1650; ^{1}H-NMR (C_6D_6, 70 °C) 1.24 (s, 9H), *ca* 1.6 (m, 4H), *ca* 3.6 (m, 2H), 4.57 (s, 1H), *ca* 7.1 (m, 5H).

***N*-[(*1R, 2R*)-1-Amino-2-phenylcyclopropyl-1-carbonyl]-(*S*)-proline (21).** A mixture of **20** (0.75 g, 2.0 mmol), MeCN (20 ml), ^{t}BuMe$_2$SiCl (0.60 g, 4.0 mmol), and NaI (0.90 g, 6.0 mmol) was stirred, under argon atmosphere, for 20 h. The mixture was then poured on a mixture of $CHCl_3/H_2O$. The aqueous phase was washed with $CHCl_3$ and the solvent was removed in vacuo. The residue was disolved in the minimum amount of water and the solution adjusted to pH = 6 with Na_2CO_3. The solid produced (compound **21**) collected by filtration and dried over P_2O_5. Yield: 0.33 g (60%), mp = 253-254 °C (dec); $[\alpha]_D$ = +74 (*c* = 0.4, EtOH); IR 3600-2850, 1690, 1570; ^{1}H-NMR (D_2O) *ca* 1.7 (m, 1H), 1.83 (dd, 1H, *J* = 6.4, *J* = 8.4), *ca* 1.85 (m, 2H), 2.01 (dd, 1H, *J* = 9.7, *J* = 6.4), *ca* 2.1 (m, 1H), 3.14 (dd, 1H, *J* = 9.7, *J* = 8.4), *ca* 3.2 (m, 2H), 4.03 (dd, 1H, *J* = 8.4, *J* = 6.9), *ca* 7.2 (m, 5H); ^{13}C-NMR (D_2O) 21.1, 24.9, 30.7, 34.0, 40.5, 47.7, 60.8, 128.9, 129.2, 129.5, 129.6, 129.9 135.3, 172.0, 176.1.

X-Ray Crystallography. The crystallography analysis is summarized in Table 2. The final atomic coordinates, lists of the structure factors, thermal components and hydrogen parameters have been deposited at the Cambridge Crystallographic Data Center.

Table 2. Crystal analysis parameters at room temperature

Crystal data	
Formula	$C_{15}H_{16}N_2O_2$
Crystal habit	Transparent plate
Crystal size (mm)	0.50 x 0.47 x 0.03
Symmetry	Monoclinic, $P2_1$
Unit cell determination	Least-squares fit from 75 reflections ($\theta < 45°$)
Unit cell dimensions	9.5322 (4), 10.4779 (4), 6.6234 (2) Å 90, 102.919 (3), 90°
Packing: V (Å^3), z	644.78 (4), 2
Dc (g.cm^{-3}), M, F(000)	1.320, 256.30, 272
μ (cm^{-1})	6.80
Experimental data	
Technique	Four circle diffractometer Bisecting geometry Graphite oriented monochromator: CuK_α $\omega / 2\theta$ scans, scan width: 1.6° Detector apertures 1.0 x 1.0°
Total measurements	Up to 65° in θ
Speed	1 min. / reflec.
Number of reflections:	
Independent	1164
Observed	1095 [3σ (I) criterion]
Standard reflections:	2 reflections every 90 minutes No variation
Solution and refinement	
Solution	Direct methods
Refinement	L.S. on F_{obs}, full matrix
Parameters:	
Number of variables	235
Degrees of freedom	860
Ratio of freedom	4.7
H atoms	Difference synthesis
Final shift/error	0.01
Weighting scheme	Empirical as to give no trends in $<w\Delta^2F>$ vs. $<\|F_{obs}\|>$ or $<\text{Sin}\ \theta / \lambda>$
Max. thermal value	U_{33} [C4"] = 0.133 (4) Å^2
Final ΔF peaks	0.12 e.Å^{-3}
Final R and R_w	0.034, 0.038
Computer and programs	VAX 11/750 XRAY76 System[29], Multan80[30]
Scattering factors	Int. Tables for X-Ray Crystallography[31]

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