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TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiopure ethyl (1*S*,9a*S*)- and (1*S*,9a*R*)-1-phenyl-4,9-dioxohexahydropyrrolo[1,2-*d*][1,4]oxazepine-9a(7*H*)-carboxylate by carbenoid/ylide/Stevens-[1,2]-shift with ring enlargement

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Abstract

Enantiomerically pure ethyl (1*S*,9a*S*)- and (1*S*,9a*R*)-1-phenyl-4,9-dioxohexahydropyrrolo[1,2-*d*][1,4]oxazepine-9a(7*H*)-carboxylate were obtained by Cu(II)-catalyzed decomposition of an α-diazo carbonyl tethered to a chiral morpholinone. The reaction occurred with moderate diastereoselectivity but with complete enantioselectivity through the carbenoid/spiro-[5,6]-ammonium ylide/Stevens-[1,2]-shift with ring enlargement sequence. © 2000 Published by Elsevier Science Ltd.

1. Introduction

The [1,2]-Stevens rearrangement of a cyclic ammonium ylide, generated by an intramolecular carbenoid attack on a lone pair of a tertiary nitrogen atoms, has potential to provide a simple general route to cyclic amines.[1] Interestingly, it has been reported that the rearrangement can proceed affording significant stereochemical retention at the migrating group,[2] in spite of mechanistic evidence suggesting radical pair intermediates.[3] In the key step of the West and Naidu synthesis of epilupinine alkaloids, this sequence has been applied by using, as a key intermediate, a spiro-[5,6]-ammonium ylide which afforded with good diastereoselectivity, but moderate enantioselectivity, 6,6-fused systems by expansion of the ring containing the migrating carbon near the nitrogen.[4]

Following our interest in enantioselective synthesis pursuing simple intramolecular cyclizations, such as metalcarbene reactions,[5] and with the aim of exploring the level of enantio- and

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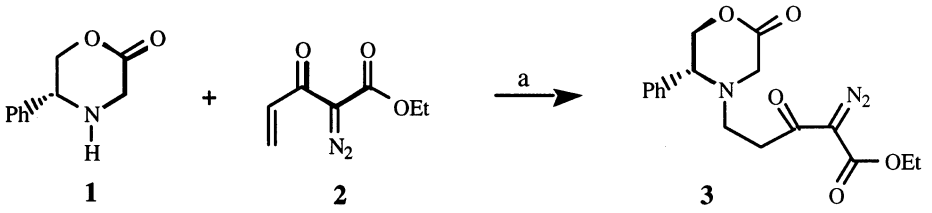
diastereoselectivity of carbenoid/ylide/Stevens-[1,2]-shift, which occurs with ring enlargement, we now wish to report the results of the catalytic decomposition of the diazocompound **1**, which bears, as a pendant, the enantiomerically pure (5*R*)-phenylmorpholin-2-one, easily obtained from the 'chiral pool'. Our aim was to obtain, by catalytic decomposition of this α-diazo-ketoester, the formation of a chiral spiro [5,6]-ammonium ylide, followed by a rearrangement to a 5,7-fused system through the asymmetric benzylic migrating group[6] and so to the simultaneous formation of a second proximal stereocentre.

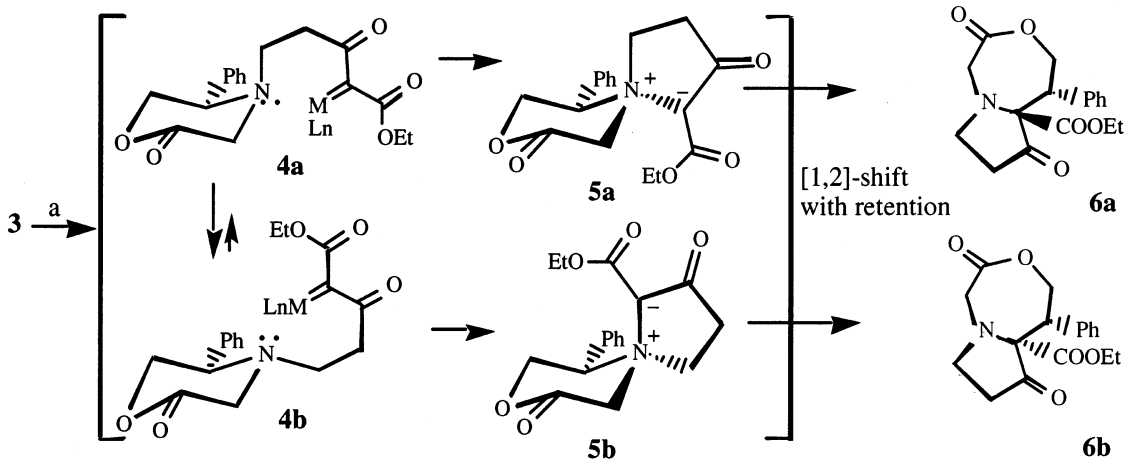
2. Results and discussion

Compound **3** was obtained in 80% yield by conjugate addition of (*R*)-5-phenylmorpholin-2-one **1** to ethyl 2-diazo-3-keto-pent-4-enoate **2** (Scheme 1). The enantiomerically pure six-membered heterocycle **1**, employed previously as a chiral template,[7] was conveniently prepared from (*R*)-2-phenylglycinol according to Dellaria.[8] The diazocompound **2**[9] was obtained by a diazo transfer reaction of the corresponding α,β-unsaturated keto ester.[10]



Scheme 1. Reagents and conditions: (a) CH_2Cl_2, rt, 80%

The copper(II)acetylacetonate-catalyzed decomposition of **3** was performed in boiling toluene until the disappearance of the diazo stretching band in the IR spectrum, providing quantitatively a 1:2 mixture of the bicyclic rearranged diastereomers **6a** and **6b**, which were easily separated because the former one is insoluble in the reaction solvent (Scheme 2).



Scheme 2. Reagents and conditions: (a) copper(II)acetylacetonate, toluene, reflux, 100%

When the decomposition of **1** was performed with rhodium(II)-based catalysts, a complex reaction mixture was obtained containing **6a** and **6b** as minor components. This result confirms the superiority of the copper(II)acetylacetonate for the carbenic generation of onium ylides.[11]

The structures of the 5,7-bicyclic diastereomers **6a**,**b** were determined from the ^{1}H and ^{13}C NMR spectra and single-crystal X-ray diffraction studies. The latter, confirming the presence of a unique enantiomer in the crystal of each diastereomer, attests to the total retention of configuration at the carbon involved in the rearrangement (Figs. 1 and 2).

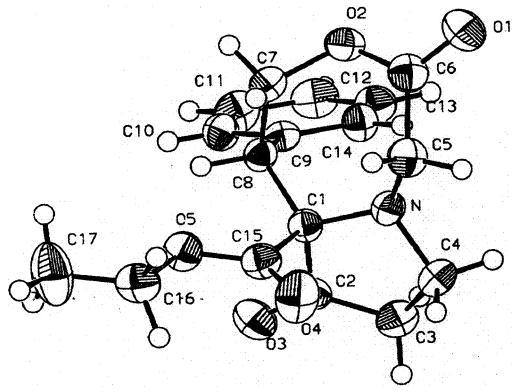


Figure 1.

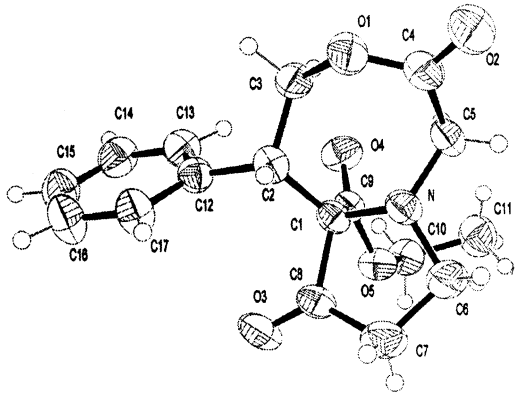


Figure 2.

The major formation of **6b**, occurring through the ylide **5b**, requires the approach of the metal carbenoid from the same face of the morpholinone ring as the phenyl substituent. This can be rationalised as a consequence of the preferential pyramidal configuration *trans* to the phenyl group assumed by the nitrogen of the related metalcarbene precursor **4b**[4] (Scheme 2). The complete retention of configuration at the migrating group is ascribed to the exclusive intramolecularity of the migration process. Therefore, the dissociation–recombination pathway involving a caged radical pair[3] can be excluded, since no traces of products arising from radical reactions were detected.

In conclusion, we have reported a case of complete enantiocontrol in a rapid construction of optically pure bicyclic skeletons by a simple route based on ammonium ylide [1,2]-shift of the chiral migrating group. This methodology demonstrates good potentialities for efficient syntheses of more elaborate policyclic targets such as alkaloid systems.

3. Experimental

3.1. General methods

Melting points were determined using a Büchi apparatus and are uncorrected. ^{1}H (300 MHz) and ^{13}C NMR spectra were performed on a Varian VXR-300 spectrometer with TMS as the internal standard. IR spectra were recorded on a Perkin–Elmer 983 Infrared spectrophotometer. The optical rotations were measured by a Perkin–Elmer 241 automatic polarimeter in a 1 dm tube. All reagents and solvents employed were reagent grade materials purified by standard methods and redistilled before use.

3.2. Ethyl 2-diazo-4-[(5R)-5-phenyl-2-oxomorpholin-4-yl]-3-oxobutanoate, **3**

A solution of the morpholinone **1** (1.6 g, 9.03 mmol) in CH_2Cl_2 (5 ml) was added dropwise to a stirred solution of **2** (1.4 g, 8.33 mmol) in anhydrous CH_2Cl_2 (20 ml). After 30 h stirring at room temperature, the solvent was evaporated and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 7:3) to give pure **3** as a low melting point solid: 2.29 g (80%), $[\alpha]_D^{25}$ −77.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.30 (m, 5H), 4.28–4.21 (m, 4H), 3.98 (d, 1H, J = 17.8 Hz), 3.69 (dd, 1H, J = 6.0, 1.95 Hz), 3.26 (d, 1H, J = 17.8 Hz), 3.03–2.89 (m, 3H), 2.47–2.38 (m, 1H), 1.30 (t, 3H, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$): δ 190.7, 167.9, 161.0, 136.1, 129.6, 128.9, 128.7, 128.2, 126.4, 72.9, 62.7, 61.5, 53.6, 49.5, 36.8, 14.3. IR (nujol): 3001, 2063, 1751, 1725, 1703, 1642, 1458, 1373, 1302, 1219, 1168, 1134, 1096, 1070 cm^{-1}. Anal. calcd for $C_{17}H_{19}N_3O_5$: C, 59.11; H, 5.55; N, 12.17. Found: C, 59.22; H, 5.66; N, 12.19.

3.3. Catalytic decomposition of **3**

Copper(II)acetylacetonate (18 mg) was added under argon to a solution of **3** (680 mg, 1.97 mmol) in anhydrous toluene (8 ml) and then the mixture was heated under reflux for 35 min. After cooling, the solution was filtered through a short column of neutral alumium oxide and then half of the solvent was evaporated in vacuo. The residue, on standing at 0°C for 1 day, formed white crystals which were collected by filtration to give pure **6a**. The mother liquor was evaporated in vacuo and the residue was purified by flash chromatography (petroleum ether:ethyl acetate = 8:2) to give pure **6b**.

3.4. Ethyl (1S,9aS)-1-phenyl-4,9-dioxohexahydropyrrolo[1,2-d][1,4]oxazepine-9a(7H)-carboxylate, **6a**

0.206 g (33%); mp 140–142°C; $[\alpha]_D^{25}$ −225 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.41–7.37 (m, 2H), 7.31–7.28 (m, 3H), 4.61–4.47 (m, 2H), 4.36–4.22 (m, 2H), 4.03 (dd, 1H, J = 6.0, 2.4 Hz), 3.98 (s, 2H), 3.58–3.39 (m, 2H), 2.38 (ddd, 1H, J = 18.3, 6.9, 1.5 Hz), 2.22–2.08 (m, 1H), 1.33 (t, 3H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 207.4, 170.8, 169.0, 135.8, 129.8, 128.4, 128.0, 69.4, 62.5, 53.6, 48.9, 46.8, 37.2, 14.2. IR (nujol): 2973, 2937, 1758, 1735, 1702, 1456, 1377, 1228, 1127, 1072, 1018 cm^{-1}. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.43; H, 6.15; N, 4.35.

3.5. Ethyl (1S,9aR)-1-phenyl-4,9-dioxohexahydropyrrolo[1,2-d][1,4]oxazepine-9a(7H)-carboxylate, **6b**

0.480 g (67%); mp 82–3°C; $[\alpha]_D^{25}$ +238 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 7.30–7.26 (m, 3H), 7.19–7.16 (m, 2H), 5.43 (dd, 1H, $J=13.2$, 9.3 Hz), 4.69 (d, 1H, $J=16.2$ Hz), 4.34 (dd, 1H, $J=13.2$, 1.8 Hz), 4.05 (m, 2H, $J=9.3$, 7.2), 3.69 (d, 1H, $J=16.2$ Hz), 3.33–3.25 (m, 2H), 3.20–3.13 (m, 1H), 2.60 (dt, 2H, $J=6.6$, 2.7 Hz), 1.08 (t, 3H, $J=7.2$ Hz). ^{13}C NMR ($CDCl_3$): δ 205.5, 171.9, 167.5, 135.4, 129.8, 129.6, 128.4, 128.2, 127.8, 71.9, 68.4, 61.6, 51.8, 47.3, 47.0, 35.8, 13.8. IR (neat): 2981, 2931, 1767, 1746, 1715, 1448, 1337, 1238, 1186, 1114, 1085, 1045 cm^{-1}. Anal. calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.31; H, 6.23; N, 4.54.

Acknowledgements

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