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Stereospecific [1,2]-rearrangement of a spirocyclic ammonium ylide with ring expansion sequence

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Abstract—Enantiomerically pure bicyclic 1,4-oxazepinone was obtained by the Cu(II)-catalyzed decomposition of an α-diazo carbonyl compound tethered to a chiral morpholinone, through the cascade evolution of the spirocyclic ammonium ylide formed. $LiAlH_4$ reduction and transesterification of the lactone moiety of the oxazepinone afforded pure chiral pyrrolidine and 3-prolinone bicyclic hemiacetal, respectively, both bearing a quaternary stereocentre. © 2003 Elsevier Science Ltd. All rights reserved.

The tandem ammonium ylide generation/rearrangement sequence has a great potential as a simple method for a rapid preparation of nitrogen heterocycles.[1]

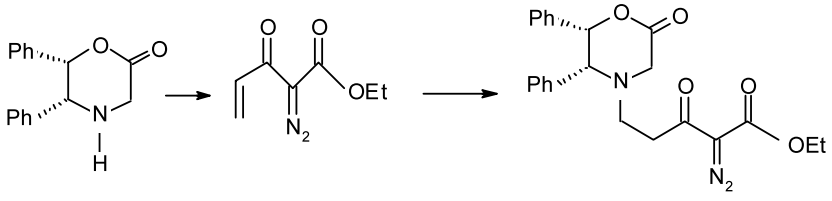
As regards chirality transfer, while in the case of the [2,3]-shift of spiro ammonium ylides important examples are known,[2] only one case of the [1,2]-Stevens rearrangement was reported by West and Naidu to proceed with remarkable diastereo- but modest enantioselectivity, in the key step synthesis of epilupinine alkaloids.[3]

Recently, following our interest in asymmetric synthesis through the carbenoid intramolecular reactivity,[4] according to this cascade methodology, we prepared 5,7-condensed bicyclic 1,4-oxazepinones, with moderate diastereo-, but complete enantioselectivity, starting from 3-oxo-2-diazopentanoate *N*-linked to (3*R*)-6-oxo-3-phenyl-4-morpholine.[5] The retention of configuration at the benzylic carbon atom involved in the [1,2]-ylide shift was observed.[6]

Herein is reported the preparation, by this protocol, of enantiopure nitrogen heterocycles of therapeutical interest.

To accomplish the [1,2]-sigmatropic rearrangement, we chose the diazocompound **3** in which the moiety bearing a diazo function is tethered to (2*R*,3*S*)-diphenylmorpholinone **1**. The latter has been previously employed, as a chiral template, in the Williams aminoacid syntheses (Scheme 1).[7]

The catalytic decomposition of **3** was expected to lead to the 5,7-bicyclic system **6** (Scheme 2), with better diastereoselectivity as in the case previously described.[5] This expectation was supported, in addition of Williams' work, also by the better asymmetric induction obtained with **1**,[8] if compared with the other chiral auxiliary mentioned.[9] The asymmetric 3-prolinone and pyrrolidine targets will be respectively obtained through the lactonic ring opening of **6** by $LiAlH_4$ reduction and by a transesterification reaction, respectively.



1 2 3

Scheme 1.

Keywords: ammonium ylide; carbenoid; ring expansion; rearrangement.
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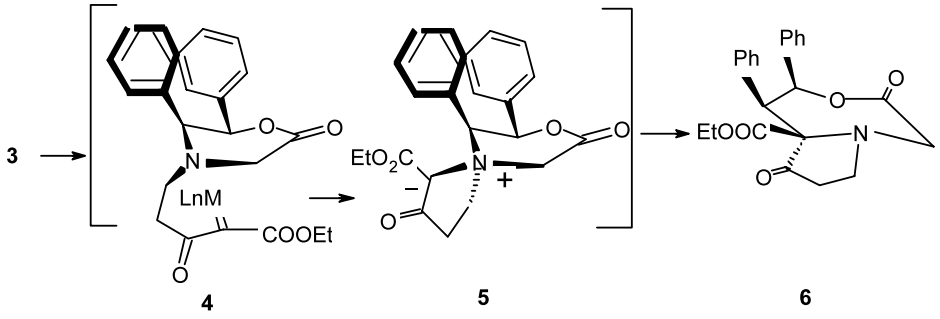
Both enantiomers and racemate of morpholinone **1** are commercially available as *N*-Boc- or *N*-Cbz- derivatives.[10] Moreover, the pure enantiomer was obtained in a less expensive way according to the procedure reported by Brussee and co-workers, who started from the convenient chiral mandelonitrile.[11] The synthesis of ethyl 2-diazo-5-[(5*S*,6*R*)-5,6-diphenyl-2-oxomorpholin-4-yl]-3-oxopentanoate **3** was performed in (79%) yield, following the procedure previous described,[4] by conjugate addition of **1** to ethyl 2-diazo-3-ketopent-4-enoate, **2**[12] (Scheme 1).

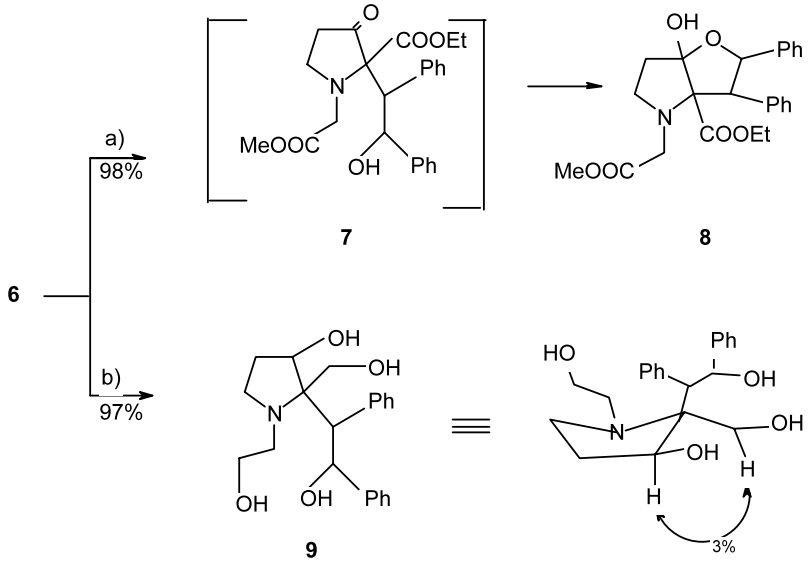
The decomposition of **3**, accomplished in boiling toluene, in the presence of 1% copper(II)acetylacetonate, was allowed to proceed until the diazo stretching band disappeared in the IR spectrum (15′); it quantitatively provided the rearranged ethyl-(1*S*,2*R*,9a*R*)-1,2-diphenyl - 4,9 - dioxohexahydropyrrolo[1,2 - *d*][1,4]oxazepine-9a-(7*H*)-carboxylate, **6**, as a single diastereomer (Scheme 2).

The superior catalytic activity of copper(II)-acetylacetonate for carbenic generation of onium ylides[13] is confirmed. However, decomposition of **3**, performed with rhodium(II)-based catalysts, afforded complex reaction mixtures containing **6** as a minor component. Transesterification of the lactone **6** in methanol, in the presence of TsOH, gave directly the bicyclic hemiacetal **8**, without traces of the expected 3-prolinone (Scheme 3). As a consequence of our failure to obtain crystals of compound **6** for an X-ray diffraction analysis, this was performed on compound **8** (Fig. 1).

Single-crystal X-ray analysis of the latter revealed the presence of a single enantiomer in the crystal, as shown by the space chiral group $P2_1$.[14] This evidence confirmed the absolute structure of the 5,7-bicycle **6**. Particularly, the absolute configuration of the quaternary carbon bearing the ester group in *cis* position to the phenyl group at the neigbouring benzylic carbon has been established. Since the quaternary carbon is not affected in the ring opening process, its absolute configuration in compound **6** is identical to that in hemiacetal **8**. Moreover, $LiAlH_4$ reduction of **6** gave the substituted pyrrolidine **9**, as a single diastereomer in which the configuration of the quaternary carbon stereochemistry is established. Finally, the remaining absolute configuration assignement to the C-3 carbon of **9** was deduced from the 2D NOESY correlation, as depicted in Scheme 3. Consequently, the formation of



Scheme 2.



Scheme 3. *Reagents and conditions*: (a) TsOH, MeOH, rt, 3 h; (b) $LiAlH_4$, THF, rt, 12 h.

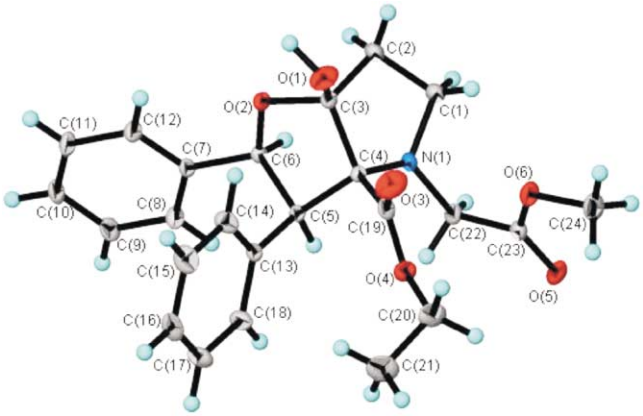


Figure 1. Atomic labelling scheme for compound **8**. The hydrogen atoms are labelled according to their parent atoms to which they are bonded (the ellipsoidal displacements are drawn at 40% probability level).

the intermediate spiranic ylide **5** can result from a carbenoid attack to nitrogen on the same face of both phenyl substituents. As a consequence of the complete retention of configuration at the migrating group, this process could still be considered intramolecular. However, a dissociation–recombination pathway involving a caged biradical could not be excluded, in spite of the fact that traces of products possibly arising from radical reactions were not detected, as in earlier examples of spiro ylides.[15]

In summary, herein is described a rapid and convenient construction of the bicyclic skeleton **6** in enantiopure form, through a cascade high asymmetric process with a radical key step.

The bicyclic 1,4-oxazepinone can be considered as a starting material to more complex systems like optically active alkaloids. Due to its convenient availability, this procedure can be extended to the (+)-enantiomer of the morpholinone **1**. Moreover, it is remarkable that in compounds **6**, **8** and **9**[16] a quaternary carbon atom is present: the construction of molecules bearing asymmetric quaternary stereocentres has represented a very challenging and dynamic area in organic synthesis over the past decade.[17]

Finally, it is noteworthy that the enantiopure heterocycle **9** fits in the class of hydroxylated pyrrolidines, potential specific and competitive inhibitors of glycosidase enzymes with application in a range of medicinal areas including anti-HIV activity.[18] The inhibition potency of this compound and its enantiomer against a variety of glycosidases will be reported in due course.

Acknowledgements

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14. Crystal data and structure refinement for **8**: single crystals were obtained by recrystallization from ethyl acetate. The substance ($C_{24}H_{27}NO_6$, $M_r=425.47$) crystallized in the monoclinic space group $P2_1$, $a=7.6394(15)$, $b=12.909(3)$, $c=11.262(2)$ Å; $\alpha=90°$, $\beta=108.57$, $\gamma=90°$; $V=1052.8(4)$ Å^3, $Z=2$, $D_{calcd}=1.342$ Mg/m^3, $F(000)=452$, $T=173$ K, crystal size 0.40×0.30×0.18 mm, $\theta=3.23°$ to 28.30°, limiting indices $=-10\le h\le 10$, $-17\le k\le 16$, $-15\le l\le 14$, reflections collected = 4888, unique = 4888 ($R_{int}=0.000$), completeness to $\theta=28.30$:99.6, refinement method: full-matrix least-squares on F^2, data = 4888, restraints = 2, parameters = 286, goodness-of-fit on $F^2=1213$, final R indices [$I>2\sigma(I)$]: $R_1=0.0561$, $wR_2=0.1327$, R indices (all data): $R_1=0.0591$, $wR_2=0.1365$, absolute structure parameter = −0.3(8), extinction coefficient = 0.379(19), largest diff. peak and hole = 0.854 and −0.882 e Å^{-3}.

Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (Deposition Number: CCDC 195180).

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16. *Data for selected compounds*: Compound **3**: Pale yellow crystals, mp 126–127°C; $[\alpha]_D^{25}=+66$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.18–7.09 (m, 6H), 7.04–7.01 (m, 2H), 6.88–6.85 (m, 2H), 5.71 (d, 1H, $J=4.2$ Hz), 4.27 (q, 2H, $J=7.2$ Hz), 4.21 (d, 1H, $J=4.2$ Hz), 3.76 (AB system, 2H), 3.14–2.96 (m, 2H), 2.90–2.73 (m, 2H), 1.31 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 190.9, 168.7, 161.1, 135.4, 134.1, 129.4, 127.9, 127.8, 126.7, 82.9, 65.5, 61.5, 51.9, 49.4, 37.1, 14.3; IR (Nujol): 2950, 2920, 2850, 2140, 1740, 1710, 1660, 1460, 1372, 1295, 1210, 1130, 1050, 715 cm^{-1}. Anal. calcd for $C_{23}H_{23}N_3O_5$: C, 65.55; H, 5.50; N, 9.97. Found: 65.21; H, 5.71; N, 9.65.
Compound **6**: White plates, mp 64–65°C; $[\alpha]_D^{25}=+77$ (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.06 (m, 10H), 5.87 (s, 1H), 4.39 (q, 2H, $J=7.8$ Hz), 4.02 (AB system, 2H), 3.62 (dd, 2H, $J=9.0$, 3.6 Hz), 2.41 (t, 1H, $J=3.9$ Hz), 2.35 (t, 1H, $J=3.9$ Hz), 2.17–2.09 (m, 2H), 1.39 (t, 3H, $J=7.8$ Hz); ^{13}C NMR ($CDCl_3$): δ 207.4, 169.9, 169.5, 138.1, 132.6, 131.2, 127.8, 127.7, 127.6, 125.7, 79.6, 68.4, 62.5, 52.7, 52.3, 49.0, 37.0, 14.3; IR (Nujol): 3849, 3419, 2360, 1742, 1601, 1522, 1492, 1455, 1376, 1334, 1302, 1222, 1177, 969, 854, 779, 756 cm^{-1}. Anal. calcd for $C_{23}H_{23}NO_5$: C, 70.21; H, 5.89; N, 3.56. Found: C, 70.42; H, 6.01; N, 3.22.
Compound **8**: White crystals, mp 137–138°C; $[\alpha]_D^{25}=-25$ (*c* 0.9, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–6.94 (m, 10H), 5.92 (s, 1H), 5.675 (d, 1H, $J=6.0$ Hz), 3.83 (AB system, 2H), 3.78 (q, 2H, $J=6.9$ Hz), 3.74 (s, 3H), 3.57 (d, 1H, $J=6.0$ Hz), 3.19 (t, 2H, $J=6.9$ Hz), 2.42 (2H, AB system), 0.76 (t, 3H, $J=6.9$ Hz); ^{13}C NMR ($CDCl_3$): δ 171.6, 170.9, 137.9, 136.2, 130.2, 127.5, 127.4, 126.5, 126.3, 126.0, 114.0, 81.89, 61.0, 57.2, 51.8, 50.6, 49.7, 39.8, 13.2; IR (Nujol): 3270, 1727, 1692, 1457, 1371, 1343, 1264, 1188, 1120, 1092, 1056, 988, 964, 848, 767, 718, 701 cm^{-1}. Anal. calcd for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40; N, 3.29. Found: C, 67.51; H, 6.28; N, 3.60.
Compound **9**: White crystals, mp 189°C; $[\alpha]_D^{25}=-90$ (*c* 0.9, CH_3OH); ^1H NMR (300 MHz, CD_3OD): δ 7.20–6.95 (m, 10H), 5.67 (s, 1H), 4.86 (s, 4H), 4.40 (dd, 1H, $J=5.7$, 4.8 Hz), 3.67–3.63 (m, 2H), 3.47–3.43 (m, 2H), 3.21–3.19 (m, 2H), 3.01–2.92 (m, 1H), 2.75 (dt, 1H, $J=9.0$, 2.4 Hz), 2.68 (dt, 1H, $J=5.4$, 12.6 Hz), 2.34–2.23 (m, 1H), 2.0–1.88 (m, 1H); ^{13}C NMR (CD_3OD): δ 145.8, 137.8, 133.7, 128.3, 128.2, 127.5, 127.4, 75.8, 72.3, 64.2, 61.3, 59.5, 52.1, 50.7, 33.1; IR (Nujol): 3816, 3707, 3668, 3646, 3563, 3495, 2362, 1646, 1600, 1492, 1374, 1340, 1288, 1261, 1229, 1204, 1174, 1142, 1100, 1086, 993, 963, 734, 611 cm^{-1}. Anal. calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.62; H, 6.36; N, 4.12.
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