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TETRAHEDRON: *ASYMMETRY*

Synthesis of enantiopure bis-isoxazolines from (4*R*)-(+)-4-acetoxycyclopent-2-enone

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Abstract—(4*R*)-(+)-4-Acetoxycyclopent-2-enone was used as a starting material in the stereoselective synthesis of enantiopure bis-isoxazolines. © 2001 Published by Elsevier Science Ltd.

1. Introduction

The introduction of defined stereogenic centres into versatile molecules is of immense importance. As such, the search for reaction pathways which stereoselectively create multiple stereogenic centres in the minimum number of steps is of great interest. Cycloaddition reactions are known to be a means of introducing stereogenic centres with defined relative stereochemistry. We have studied the reaction of nitrile oxides with 4-substituted cyclopent-2-enones to evaluate the influence of substituents on regio- and diastereoselectivities.[1] The isoxazoline products of these reactions are important since they can be transformed into γ-amino alcohols or β-hydroxy ketones and, moreover, they can exhibit useful pharmacological and biological activity.[2–14]

In the course of these studies we found that the reactions of nitrile oxides with several 4-substituted-2-cyclopentenones were completely regioselective.[1] Additionally, the reaction of 2,6-dichlorobenzonitrile oxide with 4-acetoxycyclopent-2-enone was found to be not only completely regioselective but also completely diastereoselective (see Scheme 1).[1] Thus, the 2,6-dichlorophenyl substituted cyclopentenone **9a** was seen as a promising molecule for the development of homochiral functionalised structures.

It should be noted that just prior to the completion of this study a recent paper on a closely related area was published in the literature.[15]

2. Results and discussion

(4*R*)-(+)-4-Acetoxycyclopent-2-enone[16] **11** was easily obtained from the corresponding (1*R*,3*S*)-(+)-4-cyclopentene-1,3-diol 1-acetate **10** by a literature procedure. The reaction of **11** with 2,6-dichlorobenzonitrile oxide gave only one stereoisomer, **12**, that by analogy with racemic **9a** was assigned (3a*S*,6*R*,6a*R*)-absolute configuration (see Scheme 2).

Deacetylation of **12** to introduce a new α,β-unsaturated ketone moiety for 1,3-dipolar cycloaddition with a second molecule of nitrile oxide to form bis-isoxazolines was then investigated. Deacetylation was easily accomplished by stirring the acetate in methanol at 40°C; the enantiomerically pure (3a*S*,6a*R*)-**13** was obtained in a good 80% yield.

The reaction of **13** with 2,6-benzonitrile oxide gave two regioisomeric products, **14** and **15**, in an 85:15 ratio (see Scheme 3). While ^{1}H and ^{13}C NMR spectra and elemental analysis established that compounds **14** and **15** were bis-isoxazolines, their absolute configuration was determined by single-crystal X-ray diffraction. The ORTEP plots of **14** and **15** are shown in Figs. 1 and 2.

Surprisingly, the addition of a second molecule of nitrile oxide on **13** occurred with complete diastereofacial selectivity but was not completely regioselective. The diastereofacial selectivity can be explained on the basis of steric hindrance leading to *anti*-addition. Although the major adduct **14** was that expected from a consideration of simple molecular orbital theory, the presence of both regioisomers is not easily explained.

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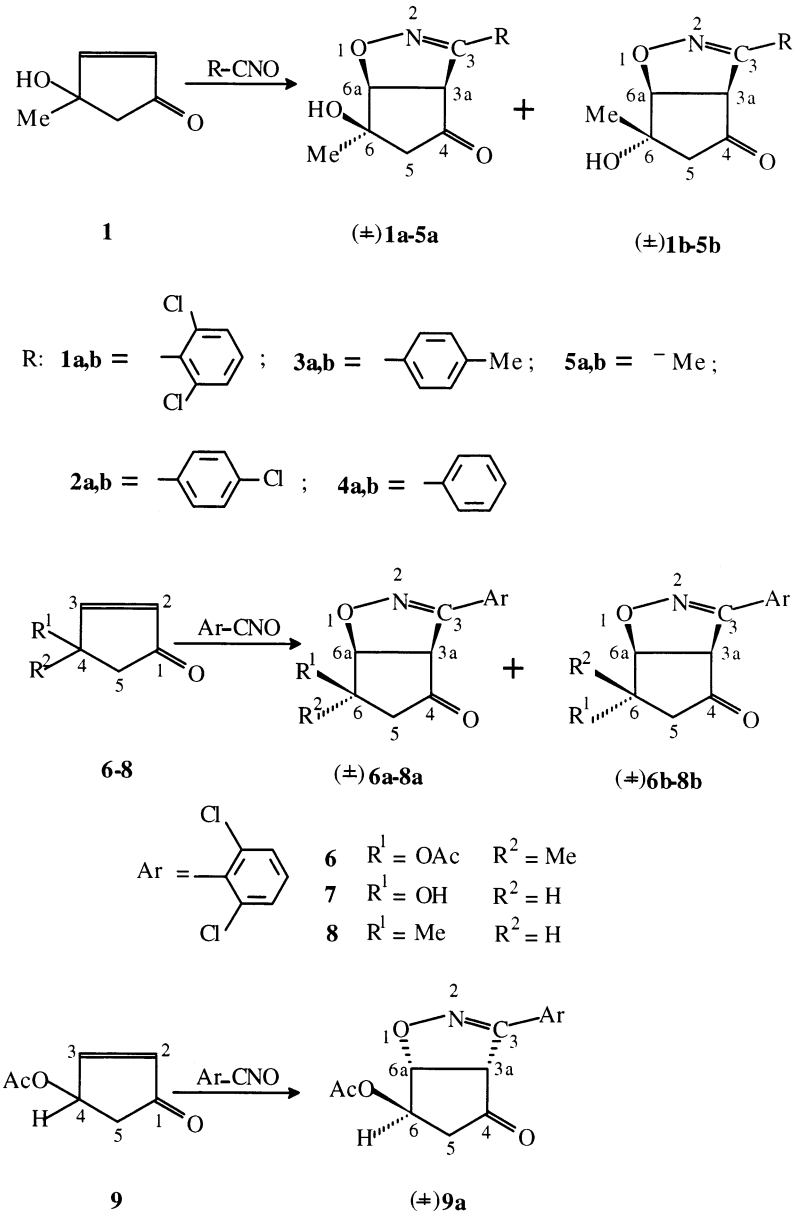
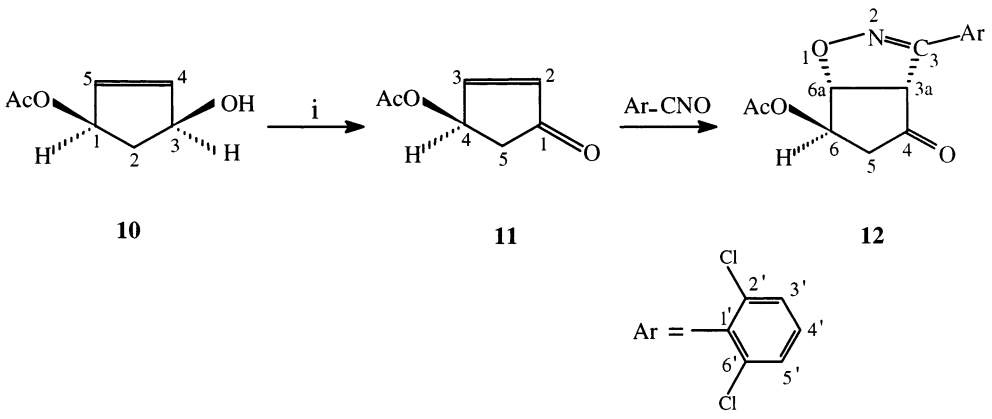
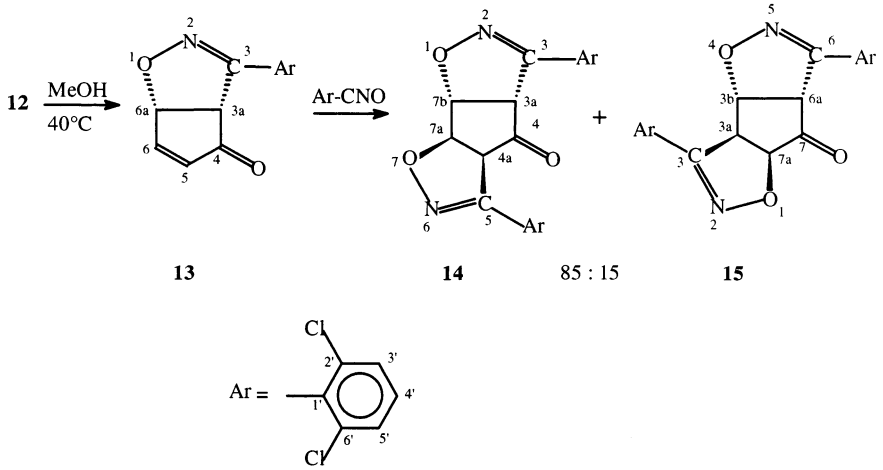


Scheme 1.



Scheme 2. i: $C_5H_5NH^+CrO_3Cl^-$, NaOAc, 4 Å sieves, CH_2Cl_2.



Scheme 3.

In conclusion, the stereogenic centre in **11** directly and indirectly controls the configuration of all other stereocentres introduced in each reaction step. The compounds obtained, **12**, **13**, **14** and **15**, lend themselves to further synthetic manipulation. To our knowledge, **14** is the first reported homochiral C_2 symmetric bis-isoxazoline with a ketone functionality. Such uncommon molecules have important applications.[17–19]

3. Experimental

3.1. General procedure

Melting points were measured on a Kofler apparatus and are uncorrected. Elemental analyses were performed on a Perkin–Elmer 240C elemental analyser. NMR spectra were recorded for $CDCl_3$ solutions on a Bruker AC 200 spectrometer (200 MHz). Chemical shifts (δ) are measured in ppm, relative to TMS as internal standard, and coupling constants (J) are in hertz. Optical rotations were determined with an optical activity instrument. Crystallographic data were collected on a Siemens P4 automatic diffractometer.

Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 70–230 mesh) were used for analytical TLC and column chromatography, respectively. Extracts were dried over anhydrous Na_2SO_4. Concentrations were performed on a rotary evaporator. Petroleum spirit refers to the fraction of distillation range 30–50°C.

(1*R*,3*S*)-(+)-4-Cyclopentene-1,3-diol 1-acetate, 99+%, was purchased from Aldrich. 2,6-Dichlorobenzonitrile oxide was prepared by dehydrohalogenation of the corresponding hydroxamoyl chloride by treatment with sodium hypochlorite.[20–22] In order to minimise its dimerisation [formation of furazan *N*-oxide (furoxan)],[23,24] the nitrile oxide was prepared directly before use and used as a solution which was added dropwise over a few minutes to the solution of the

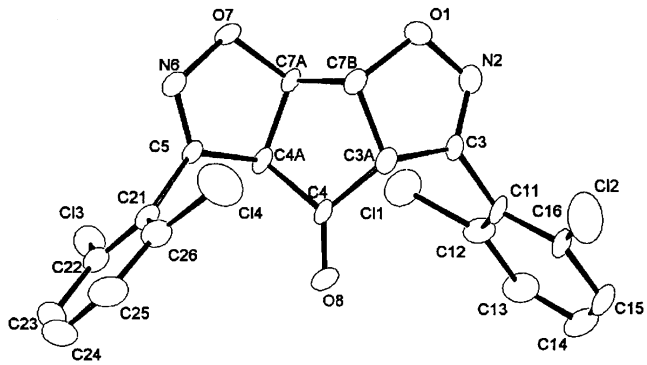


Figure 1. ORTEP drawing of the absolute configuration of compound **14**.

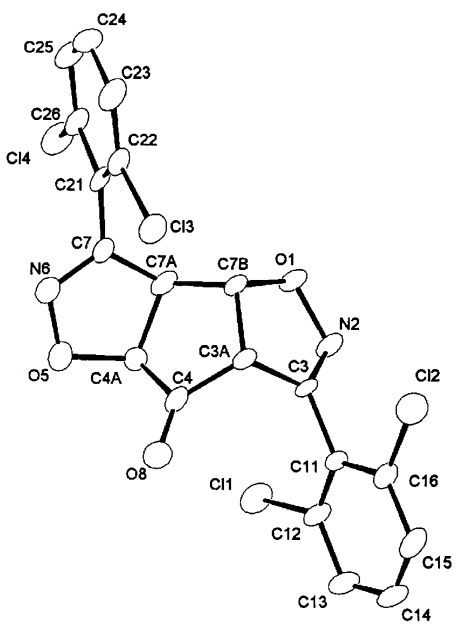


Figure 2. ORTEP drawing of the absolute configuration of compound **15**.

appropriate reagent. The furoxan was easily separated by column chromatography.

3.2. Synthesis of (4*R*)-(+)-4-acetoxy-cyclopent-2-enone 11

Compound **11** was prepared from (1*R*,3*S*)-(+)-4-cyclopentene-1,3-diol 1-acetate, **10**, according to a literature procedure.[16]

3.3. Synthesis of (3a*S*,6*R*,6a*R*)-(+)-3-(2,6-dichlorophenyl)-4-oxo-4,5,6,6a-tetrahydro-3a*H*-cyclopent[*d*]-isoxazol-6-yl acetate 12

A solution of 2,6-dichlorobenzonitrile oxide (1.68 g, 9.1 mmol) in CH_2Cl_2 (15 mL) was added dropwise to a stirred solution of **11** (0.84 g, 6 mmol) in CH_2Cl_2 (10 mL) at room temperature. The solution was stirred for 8 hours at room temperature and then concentrated. The residue was purified by flash chromatography (diethyl ether–petroleum spirit, 1:1) to give the cycloadduct **12** as a white solid (1.45 g, 74%). Mp 149.5–150.5°C (methanol). $[\alpha]_D^{20}=+319.5$ ($c=0.3$, $CHCl_3$). ^{1}H NMR: 2.02 (3H, s, CH_3); 2.44 (1H, dd, $J_{5,5'}=18.5$, $J_{5',6}=1.4$, H5′); 2.93 (1H, dd, $J_{5,5'}=18.5$, $J_{5,6}=6.1$, H5); 4.31 (1H, d, $J_{3a,6a}=9.4$, H3a); 5.43 (2H, m, H-6, H6a); 7.31–7.40 (3H, m, Ar). ^{13}C NMR: 20.8 (CH_3); 42.1 (C5); 62.3 (C3a); 73.9 (C6a); 88.2 (C6); 126.1 (C1′); 128.3 (C3′, C5′); 131.7 (C4′); 135.3 (C2′, C6′); 150.0 (C3); 169.7 (OCO); 205.5 (C4). Anal. calcd for $C_{14}H_{11}Cl_2NO_4$: C, 51.22; H, 3.35; N, 4.27. Found: C, 51.29; H 3.40; N, 4.31%.

3.4. Synthesis of (3a*S*,6a*R*)-(+)-(2,6-dichlorophenyl)-3a,6a-dihydro-4*H*-cyclopent[*d*]isoxazol-4-one 13

A solution of **12** (0.66 g, 2 mmol) in methanol (15 mL) was stirred for 1 h at 40°C and then concentrated. The residue was treated with warm petroleum spirit and the solution was filtered. Compound **13** precipitated from the solution as a white solid (0.43 g, 80%). Mp 98–99°C (methanol). $[\alpha]_D^{20}=+347.6$ ($c=0.3$, $CHCl_3$). ^{1}H NMR: 4.29 (1H, d, $J_{3a,6a}=7.4$, H3a); 5.91 (1H, dd, $J_{3a,6a}=7.4$, $J_{6,6a}=2.0$, H6a); 6.34 (1H, d, $J_{5,6}=5.7$, H5); 7.30–7.38 (3H, m, Ar); 7.65 (1H, dd, $J_{5,6}=5.7$, $J_{6,6a}=2.0$, H6). ^{13}C NMR: 59.6 (C3a); 83.9 (C6a); 126.6 (C1′); 128.1 (C3′, C5′); 131.5 (C4′); 134.5 (C5); 135.1 (C2′, C6′); 150.3 (C3); 158.3 (C6); 199.9 (C4). Anal. calcd for $C_{12}H_7Cl_2NO_2$: C, 53.73; H, 2.61; N, 5.22. Found: C, 53.79; H, 2.66; N, 5.28%.

3.5. Synthesis of (3a*S*,4a*S*,7a*R*,7b*R*)-(+)-3,5-di(2,6-dichlorophenyl)-4*H*-[1,2]oxazolo[5′,4′:3,4]cyclopenta[*d*]-[1,2]oxazol-4-one 14 and (3a*S*,3b*S*,6a*S*,7a*S*)-(+)-3,6-di(2,6-dichlorophenyl)-7*H*-[1,2]oxazolo[4′,5′:3,4]cyclopenta[*d*][1,2]oxazol-7-one 15

A solution of 2,6-dichlorobenzonitrile oxide (0.50 g, 2.7 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of **13** (0.54 g, 2 mmol) in CH_2Cl_2 (5 mL) at room temperature. The solution was stirred for 8 h at room temperature and concentrated. The residue was purified by flash chromatography (diethyl ether–petroleum spirit, 1:1) to give the cycloadducts **14** and **15** (0.76 g, 85%).

Compound **14**. White solid (0.65 g, 85%). Mp 192–193°C (methanol). $[\alpha]_D^{20}=+362.3$ ($c=0.6$, $CHCl_3$). ^{1}H NMR: 4.62 (2H, d, $J_{3a,7b}=J_{4a,7a}=9.3$, H3a, H4a); 5.75 (2H, d, $J_{3a,7b}=J_{4a,7a}=9.3$, H7a, H7b); 7.30–7.38 (6H, m, Ar). ^{13}C NMR: 62.8 (C3a, C4a); 90.1 (C7a, C7b); 125.4 (2C1′); 128.2 (4C3′); 131.9 (2C4′); 135.3 (4C2′); 148.9 (C3, C5); 201.0 (C4). Anal. calcd for $C_{19}H_{10}C_{l4}N_2O_3$: C, 50.00; H, 2.19; N, 6.14. Found: C, 50.08; H, 2.24; N, 6.20%.

Compound **15**. White solid (0.11 g, 15%). Mp 239°C, with decomposition ($CHCl_3$). $[\alpha]_D^{20}=+428.6$ ($c=0.04$, $CHCl_3$). ^{1}H NMR: 4.45 (1H, d, $J_{3a,7b}=9.6$, H3a); 4.86 (1H, d, $J_{4a,7a}=10.2$, H7a); 5.42 (1H, d, $J_{4a,7a}=10.2$, H4a); 5.57 (1H, d, $J_{3a,7b}=9.6$, H7b); 7.35–7.49 (6H, m, Ar). ^{13}C NMR: 59.8 (C7a); 62.1 (C3a); 82.7 (C4a); 83.9 (C7b); 125.5 (C1′); 126.1 (C1′); 128.5 (2C3′); 128.7 (2C3′); 132.1 (C4′); 132.2 (C4′); 135.4 (2C2′); 135.5 (2C2′); 148.7 (C3); 152.5 (C7); 205.1 (C4). Anal. calcd for $C_{19}H_{10}Cl_4N_2O_3$: C, 50.00; H, 2.19; N, 6.14. Found: C, 50.11; H, 2.25; N, 6.23%.

3.6. X-Ray structural analysis of compounds 14 and 15

Compound **14**: $C_{19}H_{10}Cl_4N_2O_3$, $M=456.09$. Trigonal, space group $P3_2$; $a=19.580(1)$, $b=19.580(1)$, $c=13.362(1)$ Å; $V=4436.4(5)$ Å^3, $Z=9$, $F(000)=2070$, $\mu=5.667$ mm^{-1}, $D_{calcd}=1.536$ g cm^{-3}, graphite monochromated (Cu-Kα) radiation ($\lambda=1.5418$ Å).

Compound **15**: $C_{19}H_{10}Cl_4N_2O_3$, $M=456.09$. Monoclinic, space group $P2_1$; $a=9.364(2)$, $b=7.978(2)$, $c=12.649(1)$ Å, $\beta=102.43(1)°$; $V=922.8(3)$ Å^3, $Z=2$, $F(000)=460$, $\mu=6.054$ mm^{-1}, $D_{calcd}=1.641$ g cm^{-3}, graphite monochromated (Cu-Kα) radiation ($\lambda=1.5418$ Å).

Data sets were collected consisting of 4369 and 1788 reflections ($2\theta_{max}=120$ and 128°) for **14** and **15**, respectively. Data were corrected for Lorentz and polarisation effects and for absorption using the Walker and Stuart method.[25] The structures were solved by direct methods of SIR-97,[26] and refined using the full-matrix least-squares on F^2 provided by SHELXL-93.[27] The final R indexes were 0.0774 and 0.0746 for **14** and **15**, respectively, for 759 and 255 refined parameters using the 4354 and 1599 reflections having $I>2\sigma(I)$. Anisotropic thermal parameters were used for all the non-hydrogen atoms. The hydrogen atoms were introduced into calculated positions and refined with an overall isotropic temperature parameter. The absolute configuration was determined for both structures, the Flack parameter[28] for the correct enantiomer being equal to 0.01(2) and 0.01(4) for **14** and **15**, respectively.

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