An Asymmetric Isoxazole Annulation

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An Asymmetric isoxazole annulation proceeds from the (*S*)-*O*-methoxyphenylalaninol imine of (*RS*)-2-phenylpropionaldehyde (**3**). Deprotonation, quenching with 4-chloromethyl-3,5-dimethylisoxazole, and hydrolysis produced isoxazolylaldehyde (**5**), whose structure was confirmed by single crystal X-ray diffractometry. The absolute configuration of (−)-**5** was established as (*R*)- by chemical correlation to the known (*S*)-(−)-4-methyl-4-phenyl-cyclohex-2-ene-1-one (**7**).

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The isoxazole annulation, elegantly exemplified by the work of Stork, is a useful method for the construction of carbocycles, which utilizes a heterocyclic ring as a latent or masked functional group [1]. Impressive advances have been recorded in the past decade in asymmetric synthesis [2], however, the preparation of chiral quaternary carbon remains a formidable challenge [3]. Our interest in natural products which contain chiral quaternary carbon in their molecular architecture [4] has led us to examine an asymmetric isoxazole annulation sequence [5], which we report herein, along with the crystal structure for the key heterocyclic intermediate.

The synthetic route is shown in the Scheme. Racemic aldehyde **1** was treated with (*S*)-*O*-methoxyphenylalaninol (**2**) [6], with azeotropic removal of water to give the imine **3**. The imine **3** was deprotonated with lithium diisopropylamide (LDA) to give, presumably, the *E*- and *Z*-lithio enamines **4**. Alkylation of the enamine **4** with 3,5-dimethyl-4-chloromethylisoxazole, followed by hydrolysis with an acetate buffer produced the isoxazolylaldehyde **5** as a crystalline solid, mp 100-102°. The structure of **5** was verified by single crystal X-ray diffractometry. Completion of the annulation sequence was accomplished by formation of the acetal **6**, hydrogenation (using either Pd on charcoal or Raney Nickel) [7], and intramolecular aldol condensation to produce 4-methyl-4-phenylcyclohex-2-en-1-one (**7**).

Scheme

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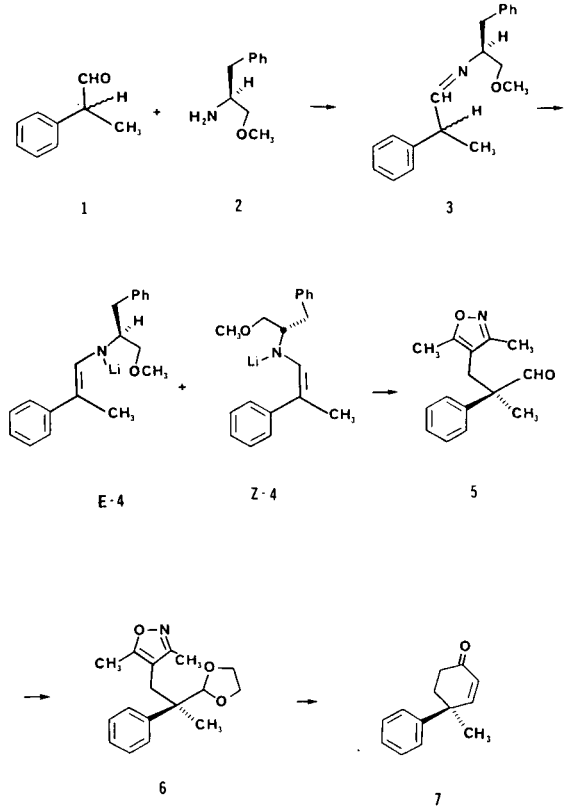

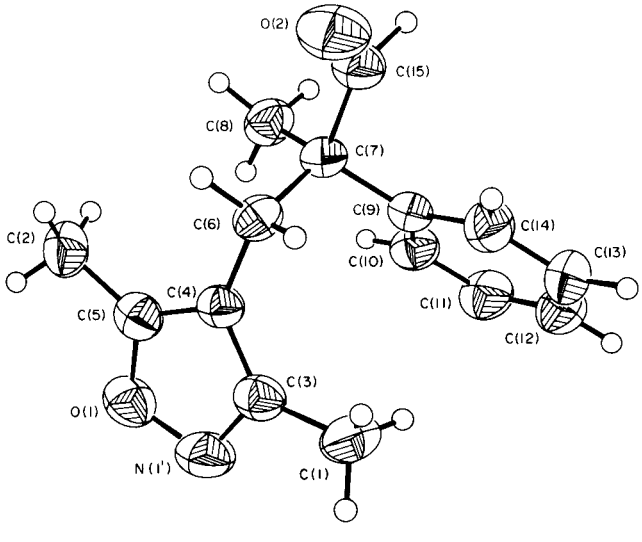

Figure. Crystal Structure of isoxazolylaldehyde **5**.

The degree of asymmetric induction was found to be critically dependent on the reaction conditions used to generate the lithio enamines **4** [8]. Thus, when deprotonation was carried out by the addition of the imine **3** to a solution of LDA in THF at 0°, the isoxazolylaldehyde **5** obtained showed $[\alpha]_D$ +9.4 (c 2.46, chloroform), which chiral LISR studies revealed to represent a 56:44 ratio (12%

Table I

Crystallographic Data

Formula	$C_{15}H_{17}NO_2$
Molecular Weight	243.31
Diffractometer	Nicolet R3/m
Crystal Class	monoclinic
a,	10.715 (1)
b,	11.277 (3)
c,	10.909 (2)
β, deg.	95.36 (1)
V, A^3	1312.51
Z	4
D, g cm^{-1}	1.23
Space Group	P 21/n
μ, cm^{-1}	0.76
F(000)	520
T, °K	298
2 θ range, deg.	3-45
no. of measured reflections	1921
no. of unique reflections with F > 3 σ(F)	1473
Largest peaks on final Fourier map, e-/A^3	+0.35, -0.27
R =	0.041
Rw =	0.048
Δ / σ	0.041

e.e.). When deprotonation was carried out *via* inverse addition (*i.e.*, addition of LDA to imine **3** at 0°, followed by warming of the solution of lithio enamines **4** to room temperature, then cooling to −78° and quenching) the isoxazolylaldehyde **5** so obtained showed $[\alpha]_D$ −58.6 (c 14.0, chloroform), which chiral LISR studies indicated to be a 15:85 ratio (70% e.e.). This material was carried on to (−)−**7**, for which Yamada and co-workers have established the (*S*)-absolute configuration [9]. Thus, we can assign the (*R*)-absolute configuration to (−)−**5**.

The sequence depicted in the Scheme represents an efficient entry into chiral isoxazolylaldehydes **5**, and 4-aryl-4-alkyl-disubstituted cyclohexenones **7**, and our future efforts will focus on the extension of this Scheme to natural products containing such an array.

EXPERIMENTAL

Synthesis of Isoxazolylaldehyde **5**.

A solution of 5.1 g of (*S*)-*O*-methoxyphenylalaninol (**2**) (0.038 mole) [6], and 6.4 g of racemic 2-phenylpropionaldehyde (**1**) (0.039 mole) in 200 ml of benzene was warmed to reflux with water removed by azeotropic distil-

Table II

Bond Lengths and Angles

C(9)-C(10)	1.389(3)	C(9)-C(7)	1.530(3)
C(9)-C(14)	1.390(3)	O(1)-N(1)'	1.410(3)
O(1)-C(5)	1.336(3)	C(4)-C(3)	1.389(3)
C(4)-C(5)	1.385(3)	C(4)-C(6)	1.500(3)
N(1)'-C(3)	1.324(3)	C(3)-C(1)	1.486(3)
C(2)-C(5)	1.485(3)	C(10)-C(11)	1.376(3)
O(2)-C(15)	1.185(3)	C(11)-C(12)	1.360(4)
C(6)-C(7)	1.548(3)	C(7)-C(15)	1.513(3)
C(7)-C(8)	1.532(3)	C(12)-C(13)	1.373(4)
C(14)-C(9)	1.390(3)	C(14)-C(13)	1.388(3)
C(9)-C(14)-C(10)	117.8(2)	C(9)-C(14)-C(7)	119.8(2)
O(1)-C(5)-N(1)'	107.2(2)	C(4)-C(6)-C(3)	127.4(2)
C(4)-C(6)-C(5)	128.4(2)	N(1)'-C(3)-O(1)	106.7(2)
C(3)-N(1)'-C(4)	111.4(2)	C(3)-C(1)-C(4)	130.7(2)
C(3)-C(1)-N(1)'	117.9(2)	C(10)-C(11)-C(9)	120.8(2)
C(11)-C(12)-C(10)	120.9(2)	C(5)-C(4)-O(1)	110.6(2)
C(5)-C(2)-O(1)	117.6(2)	C(5)-C(2)-C(4)	131.8(2)
C(15)-C(7)-O(2)	126.5(2)	C(6)-C(7)-C(4)	115.9(2)
C(7)-C(15)-C(9)	107.0(2)	C(7)-C(6)-C(9)	111.1(2)
C(7)-C(6)-C(15)	109.8(2)	C(7)-C(8)-C(9)	113.1(2)
C(7)-C(8)-C(15)	105.0(2)	C(7)-C(8)-C(6)	110.5(2)
C(12)-C(13)-C(11)	119.8(2)	C(14)-C(13)-C(9)	120.7(2)

Table III

Atomic Coordinates and Isotropic Thermal Parameters

	x	y	z	U
C(9)	3160(2)	7675(2)	0640(2)	40(1)
O(1)	0056(2)	5241(1)	−1734(2)	61(1)
N(1)'	1129(2)	5190(2)	−2195(2)	65(1)
C(4)	0952(2)	6939(2)	−1250(2)	41(1)
C(3)	1702(2)	6202(2)	−1891(2)	49(1)
C(2)	−1325(2)	6573(2)	−0644(2)	63(1)
C(10)	3352(2)	6575(2)	1200(2)	51(1)
O(2)	1738(2)	10408(1)	0240(2)	75(1)
C(11)	4507(2)	6035(2)	1260(2)	64(1)
C(5)	−0137(2)	6291(2)	−1181(2)	48(1)
C(15)	2107(2)	9580(2)	0837(2)	55(1)
C(6)	1240(2)	8176(2)	−0806(2)	44(1)
C(7)	1880(2)	8287(2)	0520(2)	42(1)
C(12)	5495(2)	6572(2)	0793(2)	67(1)
C(14)	4175(2)	8213(2)	0161(2)	56(1)
C(8)	1008(2)	7840(2)	1455(2)	55(1)
C(1)	2968(2)	6399(2)	−2307(2)	66(1)
C(13)	5339(2)	7663(2)	0243(2)	66(1)

Table IV

Anisotropic Thermal Parameters

C(9)	45(1)	36(1)	39(1)	−4(1)	3(1)	−1(1)
O(1)	69(1)	44(1)	68(1)	−4(1)	−1(1)	−7(1)
N(1)'	78(1)	53(1)	63(1)	−12(1)	5(1)	4(1)
C(4)	48(1)	39(1)	35(1)	2(1)	0(1)	5(1)
C(3)	59(1)	47(1)	40(1)	−1(1)	1(1)	4(1)
C(2)	47(1)	68(2)	73(2)	2(1)	3(1)	−5(1)
C(10)	53(1)	49(1)	52(1)	2(1)	5(1)	4(1)
O(2)	100(1)	41(1)	85(1)	1(1)	7(1)	7(1)
C(11)	65(2)	57(1)	69(2)	3(1)	−1(1)	18(1)
C(5)	54(1)	44(1)	45(1)	4(1)	−2(1)	2(1)
C(15)	61(1)	46(1)	57(1)	−8(1)	5(1)	5(1)
C(6)	45(1)	38(1)	48(1)	4(1)	6(1)	7(1)
C(7)	46(1)	37(1)	42(1)	−3(1)	6(1)	2(1)
C(12)	52(1)	72(2)	75(2)	−17(1)	−4(1)	16(1)
C(14)	52(1)	51(1)	66(1)	0(1)	10(1)	−5(1)
C(8)	54(1)	64(2)	49(1)	−3(1)	10(1)	4(1)
C(1)	66(2)	73(2)	61(2)	−13(1)	17(1)	10(1)
C(13)	45(1)	77(2)	77(2)	−14(1)	16(1)	−10(1)

Table V

H-Atom Coordinates and Isotropic Thermal Parameters

H(2a)	−1195	6522	0237	144(13)
H(2b)	−1961	6019	−0944	123(11)
H(2c)	−1586	7362	−0877	137(12)
H(10)	2671	6188	1551	57
H(11)	4617	5268	1636	72
H(15)	2600	9746	1598	59
H(6a)	1783	8532	−1354	44
H(6b)	0464	8608	−0845	44
H(12)	6298	6189	0847	75
H(14)	4071	8973	−0230	61
H(8a)	0797	7026	1285	72(7)
H(8b)	0257	8309	1394	79(7)
H(8c)	1422	7906	2271	82(8)
H(1a)	3028	7197	−2600	104(10)
H(1b)	3100	5854	−2959	115(10)
H(1c)	3592	6271	−1630	115(10)
H(13)	6036	8046	−0086	71

lation with a Dean-Stark trap until the theoretical amount of water had been collected. The solution was cooled, concentrated *in vacuo* and distilled on a short path apparatus to give 10 g of the imine **3** as an oil, bp 145° (0.75 mm Hg) (94%). One molar equivalent of LDA in 50 ml of dry THF was transferred *via* cannula to 3.9 g of the imine **3** (0.0139 mole) at 0°, and the solution was allowed to warm to room temperature over fifteen hours. The solution was then cooled to −78° and 2 ml of freshly distilled 3,5-dimethyl-4-chloromethylisoxazole (16.5 mmoles) [1c] was added, and the resulting mixture allowed to come to room temperature with stirring for twelve hours. To the resulting golden solution was added 100 ml of brine, the layers separated, and the aqueous layer extracted with methylene chloride (2 x 50 ml), and the combined organic layers concentrated and then treated with an acetate buffer (3.3 g of sodium acetate, 7.5 ml of acetic acid, 35 ml water) at 0° and allowed to come to room temperature over 24 hours. The resulting mixture was then extracted with methylene chloride (2 x 60 ml), and the combined organic layers were washed with 50 ml of 1*N* aqueous hydrochloric acid, and saturated aqueous sodium bicarbonate (3 x 50 ml), dried over anhydrous sodium sulfate, filtered and concentrated on a rotary evaporator. The resulting oil was chromatographed on silica gel (9:1 hexane:ethyl acetate) to give 1.7 g of isoxazolylaldehyde **5** as a solid (50%), $[\alpha]_D$ −58.6(c 14.0, chloroform).

Examination of the aldehyde signal of **5** by addition of $Eu(hfc)_3$ in portions showed two resonances, baseline resolved, in a 15:85 ratio. An analytical sample was obtained by sublimation on a Kugelrohr apparatus, mp 100-102°; ^1H nmr (deuteriochloroform): δ 9.57 (s, 1H), 7.26-7.36 (m, 3H), 7.05-7.07 (m, 2H), 2.798 (d, 1H, J = 15 Hz), 2.717 (d, 1H, J = 15 Hz), 1.77 (s, 3H), 1.63 (s, 3H), 1.37 (s, 3H); ^{13}C nmr (deuteriochloroform): 201.28, 166.63, 160.1, 138.71, 128.91, 127.7, 127.52, 108.8, 55.0, 29.81, 17.85, 10.66, 9.67; ir (solid, diffuse reflectance): 3063.0, 2931.8, 2816.0, 2723.5, 1722.4, 1633.7, 1450.5, 1423.5, 1199.7, 912.3, 760.0, 700.2; ms: m/z 243 (6.7 % relative intensity) 110 (100), 77 (11.5), 68 (53.8), 43 (25.3); uv: 257, 263, 289 (shoulder) nm.

Anal. Calcd. for $C_{15}H_{17}NO_2$: C, 74.04; H, 7.04. Found: C, 74.11; H, 6.92.

(*S*)(−)-4-Methyl-4-phenylcyclohex-2-en-1-one (**7**).

A solution of isoxazolylaldehyde **5** (26.6 mg, mmoles), ethylene glycol (0.1 ml) and a single crystal of *p*-toluenesulfonic acid in 25 ml of benzene was heated to reflux for four hours with water removed by a Dean-Stark apparatus. The resulting solution was concentrated on a rotary evaporator and chromatographed on silica gel (4:5:1 hexane:methylene chloride:ethyl acetate) to give the acetal **6** as an immobile oil, 29.6 mg (95%); ^1H nmr: 7.3 (s, 5H); 4.8 (s, 1H); 3.7 (s, 4H); 2.5 (s, 2H); 1.7 (s, 3H); 1.6 (s, 3H); 1.2 (s, 3H). Similarly, on a larger scale 1.6 g of **5** (6.9 mmoles) gave 1.6 g of acetal **6** (86%).

Acetal **6** was dissolved in 3% ethanolic potassium hydroxide (35 ml) in an aerosol dispersion tube, and 10% Palladium on charcoal added (100 mg). The reaction vessel was evacuated and placed under 40 psi hydrogen pressure for twelve hours. The slurry was filtered, concentrated *in vacuo*, and 20% aqueous potassium hydroxide added, and the mixture warmed to reflux for twelve hours. The reaction mixture was extracted with ether (3 x 30 ml), the combined organic layers dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was dissolved in ethanol (50 ml) and 6*N* aqueous hydrochloric acid (8 ml), and heated to reflux for four hours. The reaction mixture was cooled, water (100 ml) added, and extracted with ether (3 x 40 ml). The combined ether extracts were dried over anhydrous manesium sulfate, filtered and concentrated. The residual yellow oil was chromatographed on silica gel (chloroform) and flash distilled on a Kugelrohr apparatus to give the desired product **7**, identical in all respects with authentic racemic material, prepared according to Kane [10]. The specific rotation $-52°$ (c 1.55, ethanol) establishes the (*S*)-absolute configuration [9]. Similar results were obtained when Raney nickel was used for the hydrogenation step.

Crystal Structure of **5**.

The X-ray diffractometry conditions [5a] are summarized in Table I, the structure of **5** is shown in the Figure. The aldehyde carbonyl oxygen, O(2), is within hydrogen bonding distance of both methylene hydrogens of C(6), with O(2)-H(6a), 2.741 Å and O(2)-H(6b), 2.661 Å. Phenyl and isoxazole rings are planar, with C(10) (phenyl, 0.0062 Å) and O(1) (isoxazole, -0.0059 Å) showing the largest deviation from planarity. All three alkyl groups that are bound to the isoxazole are approximately coplanar with the ring. The deviation from planarity are -0.00513 Å for C(1), -0.0311 Å for C(2) and -0.0625 Å for C(6). The relative orientation of the plane that contains the phenyl ring with the plane that contains the isoxazole ring is 50.8°. The isoxazole oxygen and nitrogen atoms are interchangeable in the structure solution. Therefore, both atoms were fixed at half occupancy and each of their atomic coordinates and anisotropic thermal parameters treated as a free variable. Thus, the isoxazole is either freely rotating around the C(4)-C(6) bond, or the conformation of the isoxazole ring is random with respect to this axis within the unit cell constraints of the crystal. The bond lengths, bond angles, Atomic coordinates, anisotropic thermal parameters and H-atom coordinates of **5** are listed in Tables II-V. Observed and calculated structure factors (10 pages) are available from the authors.

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REFERENCES AND NOTES

[1a] G. Stork and E. Logusch, *J. Am. Chem. Soc.*, **102**, 1218 (1980); [b] G. Stork, S. Danishefsky and M. Ohashi, *ibid.*, **89**, 5459 (1967); [c] G. Stork and J. E. McMurry, *ibid.*, **89**, 5463 (1967); [d] *Idem, ibid.*, **89**, 5464 (1967).

[2] J. D. Morrison, "Asymmetric Synthesis", Academic Press, NY, a treatise in five volumes.

[3a] For recent successful approaches see: A. I. Meyers, R. Hanreich and K. T. Wanner, *J. Am. Chem. Soc.*, **107**, 7776 (1985); [b] A. I. Meyers and K. T. Wanner, *Tetrahedron Letters*, **26**, 2047 (1985); [c] A. I. Meyers, M. Harre and R. Garland, *J. Am. Chem. Soc.*, **106**, 1146 (1984).

[4] N. R. Natale, B. E. Marron and C. D. Dodson, *Synth. Commun.*, **14**, 599 (1984).

[5a] For our previous studies on the synthesis, structure and utility of isoxazoles, see: L. Schlicksupp and N. R. Natale, *J. Heterocyclic Chem.*, **24**, 1345 (1987); [b] M. Borth, K. D. Bowles, L. Schlicksupp and N. R. Natale, *J. Organomet. Chem.*, **331**, 1 (1987); [c] G. Knerr, J. I. McKenna, D. A. Quincy and N. R. Natale, *J. Heterocyclic Chem.*, **24**, 1429 (1987); [d] N. R. Natale, S. G. Yocklovich and B. M. Mallet, *Heterocycles*, **24**, 2175 (1986); [e] C. S. Niou and N. R. Natale, *Heterocycles*, **24**, 401 (1986); [f] N. R. Natale and H. Hope, *J. Heterocyclic Chem.*, **23**, 711 (1986); [g] C. K. Schauer, O. P. Anderson, D. A. Quincy and N. R. Natale, *Acta. Cryst.*, **C42**, 884 (1986); [h] K. D. Bowles, D. A. Quincy, B. M. Mallet, J. I. McKenna and N. R. Natale, *J. Chem. Ed.*, **62**, 1118 (1985); [i] N. R. Natale, J. I. McKenna, C. S. Niou, M. Borth and H. Hope, *J. Org. Chem.*, **50**, 5660 (1985); [j] N. R. Natale and C. S. Niou, *Tetrahedron Letters*, **25**, 3943 (1984); [k] N. R. Natale and D. A. Quincy, *Synth. Commun.*, **13**, 817 (1983); [l] N. R. Natale, *Tetrahedron Letters*, **23**, 5009 (1982).

[6a] A. I. Meyers, D. Williams, G. Erickson, S. White and M. Dreulinger, *J. Am. Chem. Soc.*, **103**, 3081 (1981); [b] A. I. Meyers, D. Williams, G. Erickson and S. White, *ibid.*, **103**, 3088 (1981).

[7] J. W. Scott, B. L. Banner and G. Saucy, *J. Org. Chem.*, **37** 1664 (1972), and cited references.

[8] J. Lee, T. J. Lynch, D. T. Mao, D. E. Bergbreiter and M. Newcomb, *J. Am. Chem. Soc.*, **103**, 6215 (1981).

[9a] G. Otani and S. Yamada, *Chem. Pharm. Bull.*, **21**, 2112, 2119, 2125 (1973); [b] T. Sone, S. Terashima and S. Yamada, *Chem. Pharm. Bull.*, **24**, 1273 (1976).

[10a] V. V. Kane, *Synth. Commun.*, **6**, 237 (1976); [b] M. E. Flaugh, T. A. Crowell and D. S. Farlow, *J. Org. Chem.*, **45**, 5399 (1980).