anti Selectivity in α-Chelation Controlled Hydride Addition to Acyclic Alkoxy Ketone Oximes: Preparation of Chiral Primary *anti* Amines

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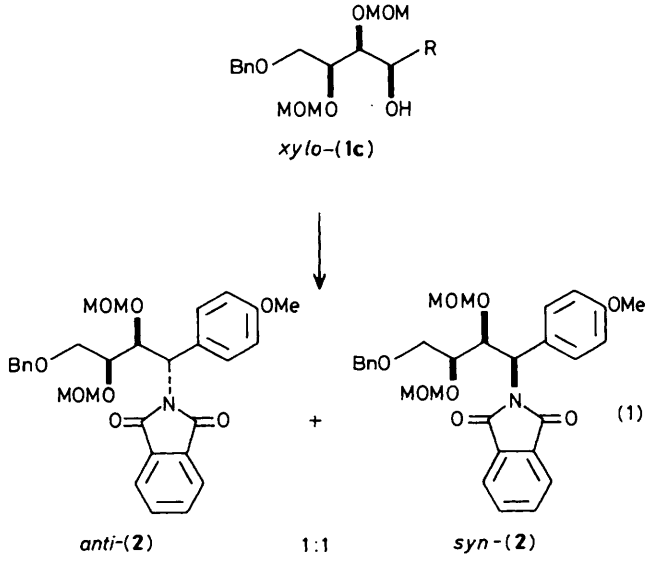
Hydride addition to acyclic α-alkoxy and α,β-dialkoxy ketone oximes using aluminium hydride reagents proceeds in an *anti*-selective manner under α-chelation control, providing chiral *anti* amines.

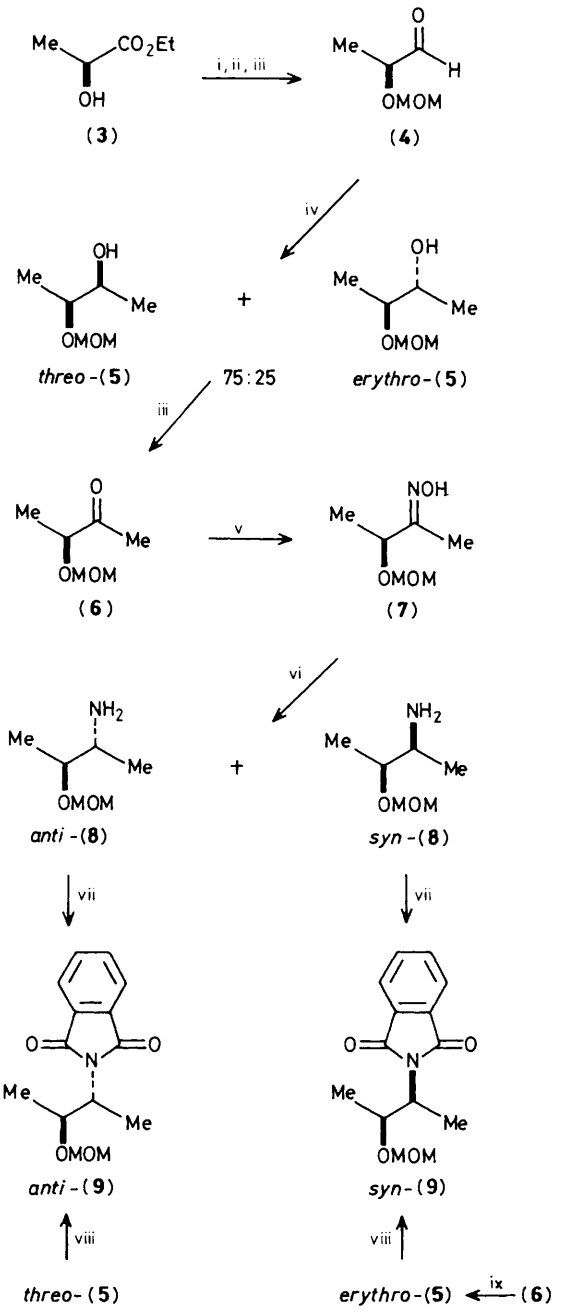
In a recent communication,[1] we reported the total synthesis of the (+)-enantiomer of natural codonopsinine. A serious problem in this synthesis was the occurrence of complete epimerization during the Mitsunobu reaction of the *xylo* alcohol (**1**) (R = *p*-$MeOC_6H_4$) to yield the phthaloyl derivatives (**2**) of the expected (4*S*)-*anti* amine along with the (4*R*)-*syn* amine in a 1:1 ratio, equation (1). At that stage it was not known which was which, though in the event one of these isomers gave (+)-codonopsinine. A simple solution to this problem would be the diastereoselective formation of *anti* amines *via* hydride reduction of a C=N group, such as that of an oxime. Stereocontrolled hydride reduction with acyclic carbonyl compounds, such as ketones, has been studied extensively in recent years;[2] however, little attention has been focused on the reaction with oximes.[3] Herein we report hydride addition to α-alkoxy and α,β-dialkoxy ketone oximes proceeding according to an α-chelation model which leads to the formation of chiral *anti* amines.

We first chose the (*S*)-α-alkoxy ketone oxime (**7**) as the substrate, which was prepared in six steps from ethyl L-lactate (**3**) as shown in Scheme 1. Thus the aldehyde (**4**) was prepared by a sequence involving methoxymethylation, $LiAlH_4$ reduction, and Swern oxidation in 53% yield from (**3**). The Grignard reaction of (**4**) afforded a chromatographically separable mixture of the alcohols *threo*- and *erythro*-(**5**) in a 75:25 ratio favouring the *threo*-isomer according to the *anti*-Cram chelation model.[4] Swern oxidation of the mixture of isomers of (**5**) yielded the ketone (**6**) (93%) which was then converted into the oxime (**7**). Reduction of (**7**) using a metal hydride such as $LiAlH_4$ or AlH_3 was found to give predomi-



a; R = Me
b; R = Pr^n
c; R = *p*-$MeOC_6H_4$

MOM = methoxymethyl ($MeOCH_2$)

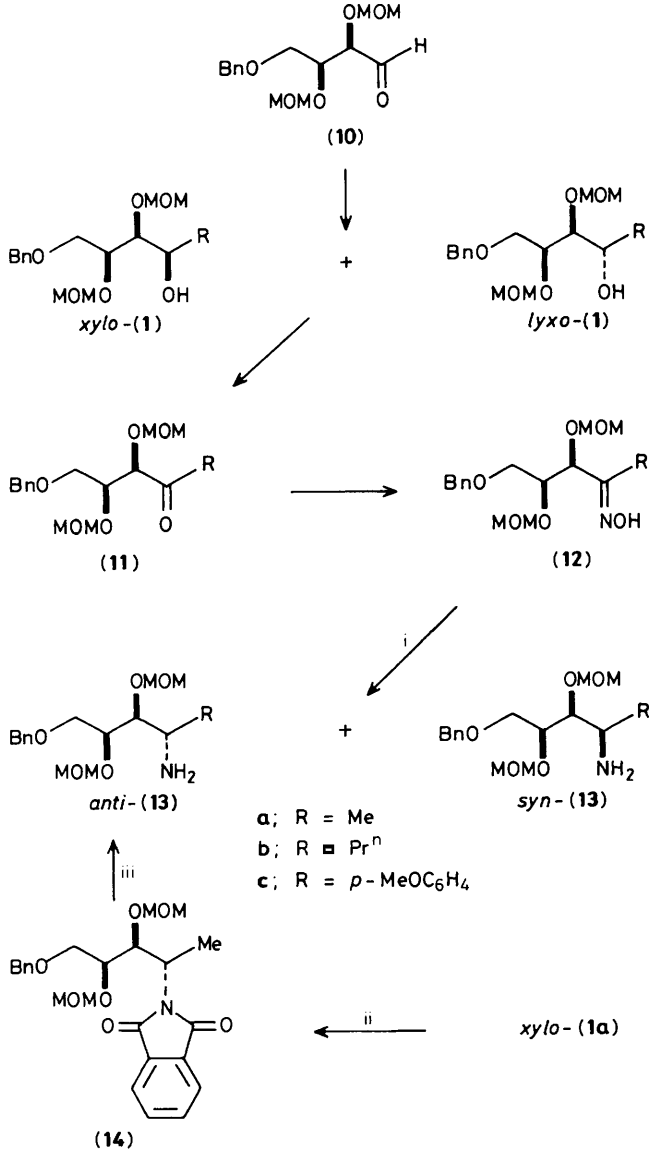


Scheme 1. *Reagents:* i, MOMCl, Pr^i_2NEt, $CHCl_3$; ii, $LiAlH_4$, tetrahydrofuran (THF)–Et_2O, 0 °C → room temp.; iii, $(COCl)_2$, Me_2SO, Et_3N, CH_2Cl_2, −78 °C; iv, MeMgX, Et_2O, 0 °C → room temp.; v, NH_2OH·HCl, pyridine, room temp.; vi, $LiAlH_4$ or AlH_3 (see Table 1); vii, phthalic anhydride, toluene, reflux; viii, phthalimide, diethyl azodicarboxylate, Ph_3P, THF, 0 °C → room temp.; ix, $Zn(BH_4)_2$, ether, 0 °C → room temp.

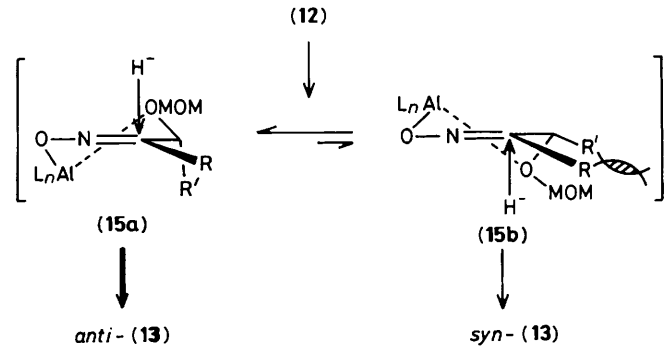
Table 1. Hydride reduction of α-alkoxy (**7**) and α,β-dialkoxy (**12a—c**) ketone oximes.

Entry	Oxime	Reducing agent	Product	*anti*:*syn* Ratio[a] (% yield)[b]	Conditions Temp. (time/h)
1	(**7**)	$LiAlH_4$	(**8**)	70:30 (78)	Room temp. (1)
2	(**7**)	AlH_3	(**8**)	69:31 (70)	Room temp. (1.5)
3	(**12a**)	$LiAlH_4$	(**13a**)	80:20 (71)	Room temp. (1)
4	(**12a**)	AlH_3	(**13a**)	75:25 (71)	0 °C (0.5) → room temp. (1.5)
5	(**12a**)	Vitride	(**13a**)	74:26 (53)	Reflux (0.5)
6	(**12a**)	DIBAL	(**13a**)	70:30 (13)	Reflux (24)
7	(**12b**)	$LiAlH_4$	(**13b**)	79:21 (65)	Room temp. (14)
8	(**12b**)	AlH_3	(**13b**)	77:23 (30)	Reflux (24)
9	(**12c**)	$LiAlH_4$	(**13c**)	81:19 (12)[c]	Room temp. (1)
10	(**12c**)	AlH_3	(**13c**)	86:14 (10)[c]	Room temp. (1.5)

[a] Determined by 400 MHz ^1H n.m.r. spectroscopy. [b] Isolated total yields. [c] Low yields of the products may be due to the accompanying formation of isomeric secondary amine(s) (*cf.* ref. 6).



Scheme 2. *Reagents:* i, aluminium hydride reagents (see Table 1); ii, phthalimide, diethyl azodicarboxylate, Ph_3P, THF, 0 °C → room temperature; iii, $NH_2NH_2 \cdot H_2O$, ethanol, reflux.



Scheme 3

nantly the *anti*-(**8**) amine in each case, as presented in Table 1 (entries 1, 2).

The stereochemistry, relative and absolute, of the major product *anti*-(**8**) was unambiguously determined by correlation with *threo*-(**5**). *anti*-(**8**) was then converted by treatment with phthalic anhydride into the phthalimide *anti*-(**9**), which was identical in all respects with the compound formed by the Mitsunobu reaction of *threo*-(**5**) with complete stereoinversion. Similarly, the stereochemistry of the minor product *syn*-(**8**) was confirmed by correlation with *erythro*-(**5**), which was obtained from ketone (**6**) by chelation controlled reduction with zinc borohydride[2,5] with a diastereoselectivity of 79:21.

We extended this methodology to the α,β-dialkoxy ketone oxime (**12**). Thus the ketones (**11**), obtained from (**10**) according to known methods,[5] were converted into the corresponding oximes (**12**) (Scheme 2). Reduction of (**12**) was carried out using a wide variety of metal hydride reagents. The results are summarized in Table 1 (entries 3—10). In all cases hydride addition occurred in an *anti*-selective manner affording predominantly the *anti*-(**13**) amines, in analogy to the *anti*-selectivity observed for (**7**). The stereochemistry, including the absolute configuration of the *anti* amine, was confirmed by correlation with *xylo*-(**1**) obtained in the diastereoselective Grignard reaction of (**10**). Thus the *anti* phthalimide (**14**) derived from *xylo*-(**1a**) by the Mitsunobu method led to *anti*-(**13a**) by treatment with hydrazine hydrate, which was found to be identical with the sample formed *via* hydride reduction of (**12**) (Scheme 2).

From the fact that nucleophilic hydride addition occurs in an *anti*-selective manner in both cases (α-alkoxy and α,β-dialkoxy ketone oximes), the direction of nucleophilic addition

is suggested to be controlled by the α- rather than the β-alkoxy group. We believe that the stereoselective transition states involve aluminium complexes in which (**15a**) is favoured over (**15b**), since the latter suffers an unfavourable $A^{1,2}$ strain[7] between R and R′ (Scheme 3). Subsequent hydride addition to the C=N bond in the conformer (**15a**) requires an antiperiplanar alignment between the developing lone pair and the approaching hydride nucleophile (from upper face),[8] thus generating the (4*S*) absolute configuration. For the formation of *anti*-(**8**) possessing the opposite configuration (*R*) with respect to the amino carbon, the same mechanism involving the antipodal transition states [the mirror images of (**15a**) and (**15b**)] should apply.

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