Reduction of Δ^2-Isoxazolines. 3.[1] Raney-Nickel Catalyzed Formation of β-Hydroxy Ketones

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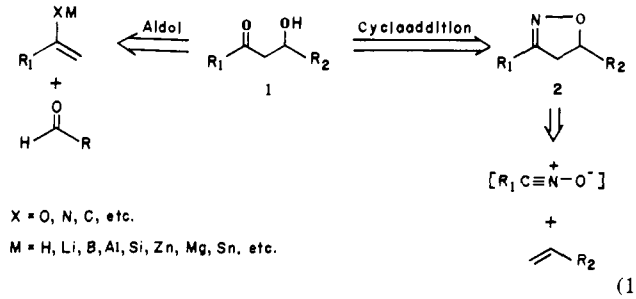
Abstract: The importance of the β-hydroxy ketone moiety has led to the development of a wide variety of aldol type methodologies for its construction. A conceptually new approach to these "aldol adducts" is presented on the basis of [3 + 2] dipolar cycloaddition of in situ generated nitrile oxides and olefins followed by reduction of the resulting Δ^2-isoxazolines. This approach provides a nice complement to the aldol type reaction. Optimum conditions for the transformation of Δ^2-isoxazolines to β-hydroxy ketones use Raney-nickel catalyst, boric acid, 5/1 MeOH/H_2O, and hydrogen gas. Under these mild conditions, 3-methyl-5-*n*-butyl-Δ^2-isoxazoline (**3a**) is transformed to 4-hydroxy-2-octanone (**4a**) in high yield. Thus "directed aldol" type adducts are readily available by selection of the appropriate olefin and nitrile oxide precursor (usually the 1° nitro compound). Advantages lie in the ready availability of precursors, the mildness of reaction conditions, the high degree of chemoselectivity and compatibility with many functional groups, and the general complimentarity to the aldol type reaction with regards to stereoselectivity and location of the new carbon–carbon bond. Most importantly, the cycloaddition–reduction sequence allows the unique possibility for *diastereospecific* formation of threo and erythro products. For example, cycloaddition of methylnitrile oxide with *trans*-2-butene gives the trans-substituted isoxazoline **8t**, which is reduced to give exclusively the threo β-hydroxy ketone **9t**. In contrast, use of *cis*-2-butene gives isoxazoline **8c** and the erythro isomer **9e** upon reduction. Here the nature of the additive was found to be most critical to prevent epimerization. It is expected that this approach will greatly expand the utility of Δ^2-isoxazolines in organic synthesis.

The aldol and related carbonyl addition and condensation reactions are of fundamental importance in organic chemistry.[3] Over the past several years, research in the area of aldol type addition reactions has not waned but, in fact, has dramatically increased. This is due in part to the large number of important natural products containing the β-hydroxy carbonyl unit. From the standpoint of synthetic strategy, the vast majority of β-hydroxy ketones are constructed by a carbonyl addition as the key carbon–carbon bond-forming reaction. As such, it is realized that the impressive array of elegant methods for formation of β-hydroxy ketones emanate largely from this single basic concept of carbonyl addition.[4] Clearly it would be desirable to develop other fundamentally different strategies that might be expected to complement the aldol type reaction. Such strategies might then have tremendous potential for applications in complex natural product synthesis.

Recently, we have begun a program directed toward the synthesis of the β-hydroxy carbonyl unit that involves cycloaddition, rather than carbonyl addition, as the key carbon–carbon bond-forming reaction. We would now like to report the details of the initial phase of our work that has resulted in a new general method for synthesis of β-hydroxy ketones.[5]

The basic strategies for β-hydroxy ketone synthesis are outlined in eq 1. Our cycloaddition strategy implements the potential synthetic equivalency of aldol adduct **1** and Δ^2-isoxazoline **2**, which are readily recognized to possess the same oxidation state along the carbon chain.[6] The advantages of the cycloaddition route



(1)

are several fold. The Δ^2-isoxazolines are readily available via well-known [3 + 2] dipolar cycloaddition of nitrile oxides with olefins.[7] The nitrile oxides in turn are generated in situ from a variety of precursors including primary nitroparaffins[8] and oximes.[7] The conditions for cycloaddition are extremely mild as opposed to the wide variety of aldol conditions that range from strongly basic to strongly acidic. The reaction is highly chemoselective. Common electrophilic (carbonyl, halide, etc.) and active hydrogen-containing (hydroxy) functional groups are tolerated without protection.[9] Rigid control over substituent stereochemistry is exercised due to the high stereospecificity of the cycloaddition reaction.[10] The sensitive β-hydroxy ketone is produced in a latent

(1) Part 2: Curran, D. P.; Singleton, D. M. *Tetrahedron Lett.* **1983**, *24*, 2079.

(2) Recipient of a Dreyfus Foundation Grant for Newly Appointed Young Faculty in Chemistry, 1981–1986.

(3) Neilsen, A. T.; Houlihan, W. J. *Org. React. (N.Y.)* **1968**, *16*, 1. House, H. O. "Modern Synthetic Reactions", 2nd ed.; Benjamin: Menlo Park, CA, 1972; pp 629–682.

(4) For an analysis of methods for formation of β-hydroxy carbonyls see: Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654. It is apparent that, with the exception of epoxide opening, all methods noted involve either direct carbonyl addition or a reaction of a precursor that is formed by carbonyl addition.

(5) A preliminary communication has appeared: Curran, D. P. *J. Am. Chem. Soc.* **1982**, *104*, 4024.

(6) (a) Most previous uses of cycloaddition reactions to form carbonyl addition substrates have revolved around the isoxazole to 1,3-dicarbonyl interconversion. Isoxazolines have the potential advantage of possessing stereochemistry in the heterocyclic ring. For leading references to isoxazole-based conversions, see: Meyers, A. I. "Heterocycles in Organic Synthesis"; Wiley Interscience: New York, 1974. Cambell, M. M. "Comprehensive Organic Chemistry"; Barton, D., Ollis, W. D., Eds.; Permagon Press: Oxford, 1979, Vol. IV, 944. Stevens, R. V. *Tetrahedron* **1976**, *32*, 1599. (b) Isoxazoles have been indirectly converted to β-hydroxy ketones by a four-step procedure. Barco, A.; Benetti, S.; Baraldi, P. G.; Guarneri, M; Pollini, G. P.; Simoni, D. *J. Chem. Soc., Chem. Commun.* **1981**, 599. Baraldi, P. G.; Fabio, M.; Pollini, G. P.; Simoni, D.; Baroc, A.; Simonetta, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2983.

(7) For an excellent review of the chemistry of nitrile oxides see: Grundmann, C.; Grünanger, P. "The Nitrile Oxides"; Springer-Verlag: New York, 1971. Caramella, P. "Comprehensive Heterocyclic Chemistry", in press.

(8) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

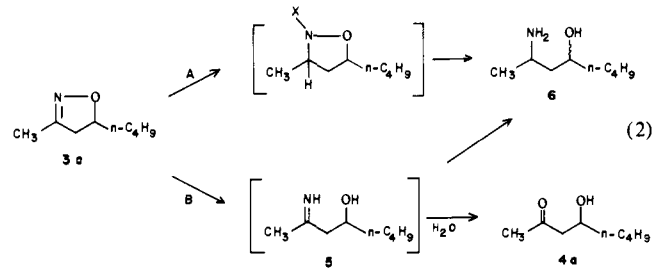
(9) Free primary and secondary hydroxyl groups cannot be employed in the Mukaiyama conditions (ref 8) due to reaction with phenyl isocyanate. However, free tertiary hydroxyl groups are tolerated (see ref 1).

(10) Bast, K.; Cristl, M.; Huisgen, R.; Mack, W.; Sustmann, R. *Chem. Ber.* **1973**, *106*, 3258.

0002-7863/83/1505-5826$01.50/0

form, as the Δ^2-isoxazoline, that can be unveiled at the desired stage. Finally, the two strategies are generally complementary with respect to carbon–carbon bond formation and stereochemistry.

A variety of isoxazoline-based synthetic conversions have been developed in the past.[11] Most commonly, reductive conditions have promoted formation of the 1,3-amino alcohol[12,13] (eq 2, path



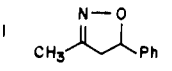
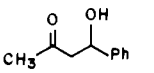
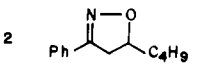
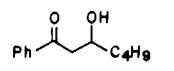
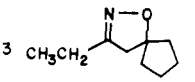
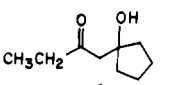
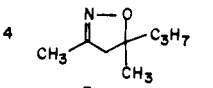
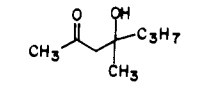
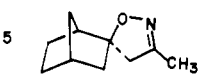
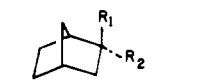
(2)

A), however, more recently several isolated examples of β-hydroxy ketone formation (eq 2, path B) have been observed.[14,15] Recently,[5] we communicated the first generally useful conditions for the metal catalyzed reduction of Δ^2-isoxazolines to β-hydroxy ketones.[16-18] We now report the full details of this initial phase of our work delineating the scope and limitations of this interconversion.

Results and Discussion

Initial experiments focused on a survey of reaction conditions using 3-methyl-5-*n*-butyl-Δ^2-isoxazoline (**3a**) as a simple substrate (eq 2). It was found that Raney-nickel catalyzed reduction of **3a** in aqueous methanol containing an acetate buffer resulted in high-yield formation of β-hydroxy ketone **4a**, presumably via hydroxyimine **5a**.[19] No amino alcohol **6** was detected. Other additives including phosphate buffers, trimethyl borate, and boric acid were also found to be most effective in this reaction. The relative merits of these additives will be discussed presently. Related nickel catalysts such as nickel boride, nickel kieselguhr, and nickel alumina were not effective in promoting reduction under similar conditions. Starting isoxazoline **3a** was recovered even after periods at reflux.

Table I

Entry	Isoxazoline	β-Hydroxy ketone	% Purified Yield
1	 **3b**	 **4b**	79
2	 **3c**	 **4c**	88
3	 **3d**	 **4d**	90
4	 **3e**	 **4e**	84
5	 **3f**	 **4f** R_1 = OH, R_2 = CH_2COCH_3 **7** R_1 = CH_2COCH_3, R_2 = OH	79

Thus, in its simplest form, the cycloaddition–reduction sequence illustrated in eq 1 provides an expedient alternative to a chemoselective cross aldol reaction between a methyl ketone and an aldehyde or ketone. While cross aldol reaction between a ketone enolate and aldehyde is relatively straightforward, employment of two ketones is more problematic.[20] Table I lists a variety of "cross aldol" adducts produced by this method. Several points are worthy of note. In all cases, crude yields were >90%. No products from retroaldol reaction or dehydration were apparent. Formation of **4b** shows that benzylic C–O bond hydrogenolysis does not compete with the desired reaction. Product **4d** is formally a regio- and chemoselective cross aldol product between methyl ethyl ketone and cyclopentanone. Thus, it can be seen that the traditional problems of enolate equilibrium, cross-condensation, and reversibility are completely bypassed by the cycloaddition–reduction approach involving methylene cyclopentane and nitropropane as cycloaddition partners. The useful stereochemical complementarity is outlined in entry 5. Cycloaddition of nitroethane with the Wittig product derived from norcamphor[21] produced **3f** as a single stereoisomer.[22] Subsequent reduction produced hydroxy ketone **4f** in good yield. In contrast, addition of allylmagnesium bromide to norcamphor, followed by Wacker type oxidation,[23] produced isomeric hydroxy ketone **7**. Thus, by nature, the two approaches are expected to give complementary results in appropriate systems with inherent bias.

To develop this cycloadditive route as a general method for control of acyclic stereochemistry,[24-26] selective formation of threo

(11) Isoxazoline-based synthetic methodologies include conversion to α,β-unsaturated ketones via β-elimination and oxime cleavage (Jäger, V.; Grund, H. *Angew Chem., Int. Ed. Engl.* **1976**, *15*, 50), conversion to β,γ-unsaturated oximes (Jäger, V.; Grund, H.; Schwab, W. *Ibid.* **1979**, *18*, 78), opening to β-hydroxy nitriles (Huisgen, R.; Cristl, M. *Chem. Ber.* **1973**, *106*, 3291. Kalvoda, J.; Kaufmann, H. *J. Chem. Soc., Chem. Commun.* **1976**, 209. Kalvoda, J.; Kaufmann, H. *Ibid.* **1976**, 210. Wade, P. A.; Hinney, H. R. *J. Am. Chem. Soc.* **1979**, *101*, 1319. Brandi, A.; DeSarlo, F.; Guarna, A.; Speroni, G. *Synthesis* 1982, 719. Kozikowski, A. P.; Adamczyk, M., submitted for publication), and cycloreversion to enol silyl ethers (Cunico, R. F. *J. Organomet. Chem.* **1981**, *212*, C51).

(12) (a) Jäger, V.; Buss, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3133. (b) Jäger, V.; Buss, V. *Liebigs Ann. Chem.* **1980**, 101. (c) Jäger, V.; Buss, V.; Schwab, W. *Ibid.* **1980**, 122. (d) Jäger, V.; Schwab, W.; Buss, V. *Angew Chem., Ind. Ed. Engl.* **1981**, *20*, 601. (e) Müller, I., Jäger, V. *Tetrahedron Lett.* **1982**, *23*, 4777. (f) Kunig, W. A.; Hass, W. *Liebegs Ann. Chem.* **1982**, 1615.

(13) For synthetic applications involving Δ^2-isoxazoline reduction to 1,3-amino alcohols see ref 12d, 12e, 12f, and 14. Also: (a) Confalone, P. N.; Lollar, E. D.; Pizzalato, G.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1978**, *100*, 6291. (b) Kozikowski, A. P.; Ishida, H. *Ibid.* **1980**, *102*, 4265. (c) Kozikowski, A. P.; Chen, Y. Y. *J. Org. Chem.* **1981**, *46*, 5248. (d) Smith, A. B., III; Schow, S. R.; Bloom, J. P.; Thompson, A. S.; Wizenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015.

(14) An indirect conversion has also been accomplished by oxidation of the resulting amino alcohol. Burri, K. F.; Cardone, R. A.; Chen, W. Y.; Rosen, P. *J. Am. Chem. Soc.* **1978**, *100*, 7069.

(15) (a) Torssell, K.; Zeuthen, O. *Acta. Chem. Scand., Ser. B* **1978**, *32*, 118. (b) Wollenberg, R. H.; Goldstein, J. E. *Synthesis* **1980**, 757. A similar reduction has recently been used in the steroid series (Kametani, T.; Furuyama, H.; Honda, T. *Heterocycles* **1982**, *19*, 357). (c) Asoaka, M.; Mukuta, T.; Takei, H. *Tetrahedron Lett.* **1981**, 735. Asoaka, M.; Abe, M.; Mukuta, T.; Takei, H. *Chem. Lett.* **1982**, 215.

(16) These reduction conditions have been advantageously employed in a short synthesis of sarcomycin; see: Kozikowski, A. P.; Stein, P. D. *J. Am. Chem. Soc.* **1982**, *104*, 4023.

(17) Recently, similar reductive conditions involving boron or aluminum additives have appeared. (a) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123. (b) Martin, S. F.; Dupre, B. *Ibid.* **1983**, *24*, 1337.

(18) Other modes of cleavage include ozonolysis (see ref 17a) and titanium trichloride. Anderson, S. H.; Das, N. B.; Jorgenson, B. D.; Kjeldsen, G.; Knudsen, J. S.; Sharma, S. C., Torssell, K. B. G. *Acta. Chem. Scand., Ser. B* **1982**, *36*, 1.

(19) In no case have we been able to isolate the intermediate hydroxyimine.

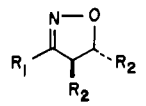
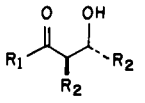
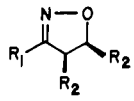
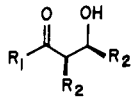
(20) For a selection of methodologies useful for directed aldol reaction see: Wittig, G. *Fortschr. Chem. Forsch.* **1976**, *67*, 1. Stork, G.; Kraus, G. A.; Garcia, G. A. *J. Org. Chem.* **1974**, *39*, 3459. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503. Corey, E. J.; Enders, D. *Tetrahedron Lett.* **1976**, 3. Kuwajima, I.; Sato, T.; Arai, M.; Minami, N. *Ibid.* **1976**, 1817. Murata, S.; Sizuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248.

(21) Prepared from norcamphor with $Ph_3P^+CH_3\ Br^-$, KO*t*-Bu, THF. We thank S.-C. Kuo for preparation of this olefin.

(22) Brown, H. C.; Hammar, W. J.; Kawakami, J. H.; Rothberg, I.; Jagt, D. L. V. *J. Am. Chem. Soc.* **1967**, *89*, 6381.

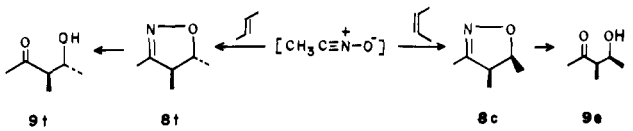
(23) Tsuji, J.; Shimizu, I.; Yamamoto, K. *Tetrahedron Lett.* **1976**, 2975.

Table II

Isoxazoline	Product	% Purified Yield
		
8t $R_1=R_2=CH_3$	9t	83
10t $R_1=CH_3$; $R_2=n\text{-}C_3H_7$	11t	79
12t $R_1=Ph$; $R_2=CH_3$	13t	70
		
8c $R_1=R_2=CH_3$	9e	77
14c $R_1=CH_3$; $R_2,R_2=[CH_2]_4$	15e	87
16c $R_1=CH_3$; $R_2,R_2=[CH_2]_3$	17e	97[a]
12c $R_1=Ph$; $R_2=CH_3$	13e	73

[a] Crude yield.

and erythro β-hydroxy ketones was investigated.[27] In the aldol approach, the stereochemistry is determined by the relative energy of the various possible transition states or the reversibility of the reaction. Since [3 + 2] dipolar cycloadditions between nitrile oxides and olefins are well-known to be 100% stereospecific,[10] our cycloaddition–reduction sequence allows the possibility for *diastereospecific* formation of β-hydroxy ketones as shown in eq 3. In principle, the relative stereochemistry (threo or erythro)

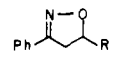
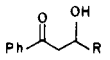
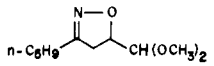
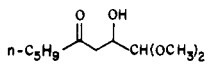


(3)

is determined only by the geometry of the starting olefin (trans or cis).[28] The utility of this strategy is enhanced by the wide range of methods for selective synthesis of cis and trans olefins.

To reduce such a scheme to practice, hydrogenolysis conditions were required that would avoid any loss of carefully obtained stereochemistry. This was investigated with *trans*-2-butene adduct **8t**. Using initially developed reduction conditions, the reaction proceeded smoothly as anticipated; however, small but significant amounts of erythro product **9e** contaminated the expected threo product **9t** as determined by 300-MHz NMR of the crude reaction mixture (**9t**/**9e**, 91/9). Thus, control over stereochemistry was to some degree lost by epimerization. Although phosphate buffers exhibited noticeable improvement over their acetate counterparts (**9t**/**9e**, 94/6), it was found that borate additives were most successful. Initial experiments focused on the use of trimethyl borate. Careful ^{1}H-NMR analysis showed the presence of ~1.5% epimerized product **9e** in the crude reaction mixture. Appropriate control experiments[29] showed that both the starting Δ^2-isoxazolines and the product β-hydroxy ketones retained their stereochemical integrity under the reaction conditions. By assumption that the intermediate β-hydroxyimine[19] was the species undergoing epimerization, a general set of reaction conditions was designed to maximize the rate of hydrolysis of the imine by increasing the water concentration and employing a slightly more acidic borate. Thus, optimum reaction conditions for suppression of epimerization involve use of H_2 (1 atm, balloon), 5/1 MeOH/H_2O, 2–5 equiv of $B(OH)_3$, and a small amount of Raney-Ni catalyst. Under these conditions, **8t** is reduced to **9t** without formation of a detectable amount of **9e**. Similarly, **8c** is cleanly reduced to **9e**. Applying these optimum conditions, a wide variety of adducts were reduced without detectable epimerization (Table II). Again, crude yields were generally greater than 90%, and purified yields were uniformly high. Reaction times from 15 min to 3 h at room temperature were generally sufficient. Most importantly, employing these conditions, *in no case were we able to detect any loss of stereochemical purity*!

Table III

Entry	Isoxazoline	Product	% Purified Yield
			
1	18a R = CH_2OH	19a	71
2	18b R = $CH_2OSi(t\text{-}but)Me_2$	19b	83
3	18c R = CH_2OTHP	19c	84
			
4	18d	19d	90

To illustrate the mildness of the reaction conditions, the survivability of several common acid-sensitive protecting groups was investigated as outlined in Table III. Both *tert*-butyldimethylsilyl and tetrahydropyranyl ethers (entries 2 and 3) remain intact. For comparison, authentic diol **19a** was generated by reduction. No evidence for diol **19a** was found in either case. Acetals are also preserved as demonstrated by high-yield formation of **19d**.[30] Thus, all functional groups stable in aqueous media at near neutral pH (~5.5–6) can be expected to survive the mild reaction conditions provided they are not reduced by Raney nickel.

Hydrolysis of substituted β-hydroxyimines is often complicated by retroaldol type reactions.[31,32] In no case so far presented did we detect any evidence for these products and formation of more than trace amounts is precluded by high yields of hydroxy ketone. To further investigate this question, we choose stilbene adducts **20t** and **20c** as systems known to be prone to facile retroaldol reaction.[32] Reduction of **20t** with acetate or phosphate buffers or trimethyl borate gave **21t** along with small amounts of **21e** and substantial amounts (20–60%) of the retroaldol products, benzaldehyde and phenyl acetone (see eq 4). However, employing optimum conditions, exclusive formation of **20t** was observed with no detectable amount of benzyaldehyde or phenyl acetone. Again it is evidenced that undesired side reactions are suppressed. As

(24) For a review of the general problem of acyclic stereoselection including aldol diastereoselection, see: Bartlett, P. A. *Tetrahedron* **1980**, *36*, 3.

(25) Several recent contributions in this rapidly growing area include: Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk. A.; Garvey, D. S. *Ibid.* **1981**, *103*, 1568. Evans, D. A.; Bartroli, J.; Shih, T. *Ibid.* **1981**, *103*, 2127. Evans, D. A.; Bartroli, J. *Tetrahedron Lett.* **1982**, *23*, 807. Heathcock, C. H.; Pirrung, M. C.; Montgomery, S. H.; Lampe, J. *Tetrahedron* **1981**, *37*, 4087. Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278. Noyori, R.; Nishida, I.; Sakata, J. *Ibid.* **1981**, *103*, 2106. See also: Mukaiyama, T. *Org. React. (N.Y.)* **1982**, *28*, 203. Evans, D. A.; Nelson, J. V.; Taber, T. R. *Top. Stereochem.* **1982**, 13.

(26) A related approach on the basis of addition of allyl organometallics to aldehydes and subsequent Wacker oxidation or ozonolytic cleavage of the resultant olefin has been investigated by several groups. See: Hoffmann, R. W.; Zeiss, H. J. *J. Org. Chem.* **1981**, *46*, 1309 and references cited therein.

(27) The cyclocondensation approach of Danishefsky involving formation and cleavage of γ-pyrones may be considered as a cycloadditive route; however, analogies with carbonyl addition are clear (Danishefsky, S. A.; Kato, N.; Askin, D.; Kerwin, J. F., Jr. *J. Am. Chem. Soc.* **1982**, *104*, 362). For an elegant approach involving [2 + 2] Paterno–Buchi photocycloaddition of furans and aldehydes see: Schreiber, S. L.; Hoveyda, A. H.; Wu, H.-J. *J. Am. Chem. Soc.* **1983**, *105*, 660. Here again, the aldol type dissection is employed.

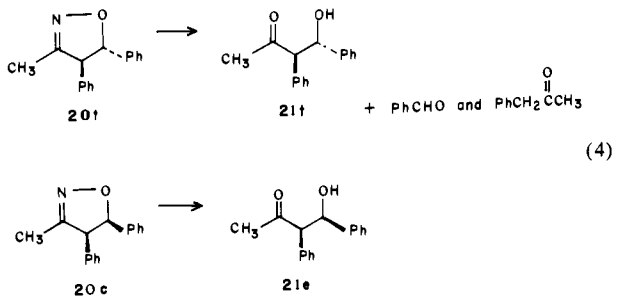
(28) Opening an epoxide, for example, by cyanide, is another example of a diastereospecific formation of β-hydroxy carbonyls. See ref 4.

(29) These control experiments were performed on the cyclopentyl adducts that were much more susceptible to epimerization.

(30) This experiment was performed by C. Fenk. These compounds can readily be cyclized to form γ-hydroxycyclopentenones (D. P. Curran, submitted for publication).

(31) A. I. Meyers, personal communication. It is suspected that the β-hydroxyimine is the species undergoing retroaldol cleavage.

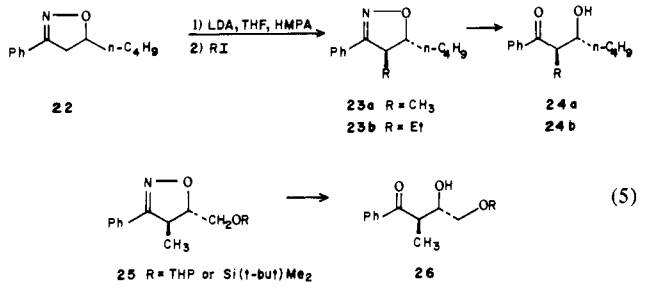
(32) For a related system see Fuchs, P. L. *J. Org. Chem.* **1976**, *41*, 2935.



(4)

adduct **20c** was even more prone to retroaldol reaction, cleavage was not completely eliminated. Under optimum conditions, **21e** was formed along with the retroaldol products in a ratio of 91/9.[33] Thus, all but the most sensitive systems should be susceptible to clean reduction.

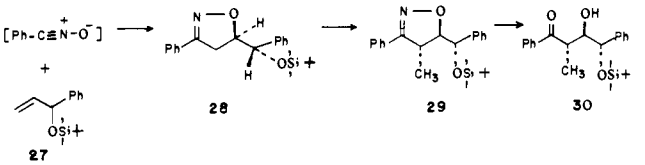
Limitations that exist in this methodology primarily derive from the cycloaddition step. For example, yields frequently diminish with increasing olefin substitution in the absence of activating groups.[7] With intermolecular cycloadditions employing aliphatic nitrile oxides our experience has been that, while yields with 1,1- and trans-disubstituted olefins are acceptable, cis-disubstituted olefins give much lower yields. Unactivated trisubstituted olefins are not generally useful as reaction partners. In addition, regioselectivity in the 1,2-disubstituted case is usually low to moderate depending on the activating nature of the substituents.[7] Similar alkyl groups offer essentially no regiochemical bias. This regiochemical problem is nicely overcome using alkylative chemistry of Δ^2-isoxazolines that has been developed by Jäger[34] (eq 5). For example, treatment of **22** with LDA/HMPA (−78 °C)



(5)

generates the corresponding endo anion.[35] Jäger has shown that, while expected β-elimination occurs upon warming, at −78 °C the anion can be nicely trapped with reactive electrophiles. Addition of methyl iodide produces **23a**, along with the cis isomer, as a 12/1 mixture of stereoisomers. Standard hydrogenolysis–hydrolysis then produces threo adduct **24a** in 91% yield. Similarly, ethyl adduct **23b** produces **24b**, and **25** produces **26**, suitable for further functionalization. At present, only threo adducts are available via this route. Attempts to generate erythro adducts via kinetic protonation were unsuccessful due to the apparent inability to abstract the relevant methyne proton.[36]

This methodology can be combined with recent developments in the field of 1,2-asymmetric induction in cycloadditions[37] to allow for formation of three consecutive chiral centers with moderate overall stereocontrol (eq 6). Thus, cycloaddition of phenylnitrile



(6)

oxide with olefin **27** produced **28** and its diastereomer in a ratio of 77/23.[38a,b] Jäger type alkylation of the major isomer produced **29**[38b] and the cis isomer (86/14). Finally, reduction of **29**, produced β-hydroxy ketone **30**.

Intramolecular nitrile oxide–olefin cycloadditions are not subject to the aforementioned limitations as yields are excellent and regiochemistry is controlled by the length of the intervening chain.[39] As such, synthetic applications involving intramolecular cycloaddition and reduction appear particularly promising, and a variety of intramolecular cycloadducts were investigated as listed in Table IV. Details for preparation of the cycloaddition substrates are given in the Experimental Section. Again it is noted that no detectable loss of stereochemistry was observed in the reduction step. The possibility that small amounts of epimerization (<2%) may occur is not ruled out. This is particularly noteworthy in the cyclopentyl series (entries 3 and 6) where substantial epimerization occurred under other conditions. This can be attributed to the well-known stability of endocyclic olefins in the cyclopentyl series, effectively facilitating imine–enamine tautomerization. Also of interest is entry 7 involving intramolecular cycloaddition with a trisubstituted olefin. As expected, entropic factors greatly facilitate this reaction and a high yield of cycloadduct **35** is obtained. Clean reduction gives β-hydroxy ketone **36**, formally the product of a stereoselective cross aldol reaction between two ketones! A transformation such as this using aldol type methodology[40] is most difficult since this approach relies largely upon steric differences in the two substituents of the electrophilic partner for its diastereoselectivity. Thus, while aldehydes are frequently excellent partners, ketones are often poor.

Combination of this new methodology with important existing classes of carbon–carbon bond-forming reactions is expected to provide new annulative methods. Potential applications involving Claisen rearrangement,[41] Diels–Alder reaction, Pd(O)-catalyzed allylic alkylation, and aldol type reactions[30] may be envisioned.

Finally, the utility of other catalysts was briefly investigated using the standard reaction conditions ($B(OH)_3$, 5/1 MeOH/H_2O). Indeed, 10% palladium on carbon is a most effective catalyst as indicated by the results collected in Table V. Again, the importance of the boric acid was clearly demonstrated as other additives (AcOH) produced substantial amounts of amino alcohol with Pd–C. As before, no detectable loss of stereochemistry was observed. Prereduced platinum oxide was also an effective catalyst under these conditions for several substrates; however, longer reaction times were required for complete conversion and on several occasions the yields were significantly lower.

Conclusion

Optimum conditions for the Raney-nickel catalyzed hydrogenolysis–hydrolysis of Δ^2-isoxazolines have been presented. Coupled with the formation of Δ^2-isoxazolines via nitrile oxides and olefins, this cycloaddition–reduction strategy may be expected

(33) This reduction was performed at 0 °C to minimize retroaldol reaction. In a similar experiment at room temperature the ratio of hydroxy ketone to retroaldol products was 85/15.

(34) (a) Jäger, V.; Schwab, W. *Tetrahedron Lett.* **1978**, 3129. (b) Grund, H.; Jäger, V. *Liebigs Ann. Chem.* **1980**, 80.

(35) 3-Phenyl substituents were chosen to eliminate the possibility of exo anion generation; however, precedent exists for the possibility of generating either exo or endo anions depending upon reaction conditions. Lidor, R.; Shatzmiller, S. *J. Am. Chem. Soc.* **1981**, *103*, 5916.

(36) This anion has been generated, but only in the absence of 5-substitutents, see ref 34. For formation of cis products see ref 17b.

(37) Caramella, P.; Rondan, N. G.; Paddon-Row, M. N.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 2438. Frank, R. W.; John, T. V.; Olejniczak, K.; Blount, J. F. *Ibid.* **1982**, *104*, 1106. Kozikowski, A. P.; Ghosh, A. K. *Ibid.* **1982**, *104*, 5788. Moses, S.; Houk, K. N.; Schohe, R.; Jäger, V.; Fronczek, F. R., submitted for publication.

(38) (a) The author thanks Prof. K. N. Houk and S. Moses for a sample of olefin **27** and helpful discussions regarding the 1,2-asymmetric induction. (b) The stereochemistry of **28–30** was assigned by precedent only and should be regarded as tentative.

(39) Garanti, L.; Sala, A.; Zecchi, G. *J. Org. Chem.* **1975**, *40*, 2403. Jäger, V.; Gunther, H. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 246. Kozikowski, A. P.; Chen, Y. Y. *Tetrahedron Lett.* **1982**, *23*, 2081. See also ref 13.

(40) For isolated examples of this type of aldol reaction see: Fellmann, P.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 1349. Stevens, R. W.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* **1982**, 1459. Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972.

(41) D. P. Curran and P. Jacobs, unpublished observations from these laboratories.

Table IV

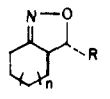
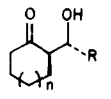
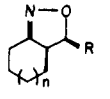
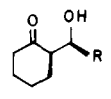
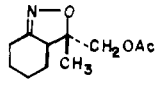
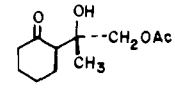
Entry	Isoxazoline	Product	% Purified Yield
			
1	**31a** R = CH_3, n = 1	**32a**	85
2	**31b** R = Ph, n = 1	**32b**	73
3	**31c** R = CH_3, n = 0	**32c**	84
			
4	**33a** R = CH_3, n = 1	**34a**	90
5	**33b** R = Ph, n = 1	**34b**	74
6	**33c** R = CH_3, n = 0	**34c**	86
			
7	**35**	**36**	82

Table V. Pd–C, $B(OH)_3$ Reduction

isoxazoline	β-hydroxy ketone	% yield
3a	4a	95
14c	15e	94
31a	32a	98
31b	32b	66
33a	34a	88
33b	34b	57

to provide the first general alternative to the aldol type reaction for formation of β-hydroxy carbonyls. Advantages lie in mildness of the reaction conditions, the high degree of chemoselectivity and compatibility with many functional groups, and the general complementarity to the aldol type reaction with regards to stereoselectivity and location of the newly formed carbon–carbon bond. Most importantly, the cycloaddition–reduction sequence allows the unique possibility for *diastereospecific* formation of threo and erythro products. Δ^2-Isoxazolines may now be routinely considered as heterocyclic aldol equivalents, and it is expected that this will greatly expand their synthetic utility.

Experimental Section

General. All melting points and boiling points are uncorrected. Kugel–Rohr boiling points refer to oven temperature. All reactions were run under nitrogen atmosphere with the exception of reductions that were conducted under hydrogen. Olefins employed were commercially available unless otherwise indicated. Reagents and solvents were purified as follows: CH_2Cl_2, distilled from CaH_2; benzene, distilled from sodium; ether and tetrahydrofuran, distilled from sodium/benzophenone; phenylisocyanate, vacuum distilled (aspirator); triethylamine, distilled from CaH_2 and stored over KOH.

Initial experiemnts involved the use of commercially available Raney-Ni (Alpha Inorganics) after careful washing, however, W-2 Raney nickel prepared according to ref 42 was shown to effect faster reaction rates. The catalyst was carefully washed free of hydroxide with 20–30 water washes (stir–decant) and stored at −20 °C under methanol. Good activity was maintained up to about 6 mo.

3-Methyl-5-*n*-butyl-Δ^2-isoxazoline (3a) (Mukaiyama Procedure; Method A).[8] To a solution of 1-hexene (37 mL, 0.33 mol) and phenyl isocyanate (21.8 mL, 0.20 mol) in dry benzene (50 mL) was added a solution of nitroethane (8 mL, 0.11 mol) and triethylamine (20 drops, catalyst) in benzene (30 mL) over 10 min. After the mixture was stirred for 1 h at 23 °C, the reaction was refluxed for 1 h. After it was cooled, the thick slurry was diluted with ether (250 mL) and filtered. Upon concentration of the filtrate, the residue was distilled (bp 45–48 °C, 0.2 mm) to give **3a** (12.7 g, 90%) as a pale yellow oil: ^1H NMR δ 4.53 (1 H, m), 2.97 (1 H, ddd, J = 17, 10, 0.8 Hz), 2.55 (1 H, ddd, J = 17, 8, 0.8 Hz), 1.98 (3 H, narrow t, J = 0.8 Hz), 1.8–1.2 (6 H, br), 0.92 (3 H, t).

4-Hydroxy-2-octanone (4a) (Method 1). To a solution of **3a** (1.41 g, 10 mmol) in 15/1 methanol/water (16 mL) was added buffer (1.5 mmol NaOAc/HOAc) and a spatula tip of Raney nickel. By means of a balloon attached to a three-way stopcock, the vessel was evacuated and flushed with hydrogen gas 5 times. After the mixture was vigorously stirred for 3 h at 23 °C, the reaction was filtered through Celite into a separatory funnel containing dichloromethane/water. After separation, the aqueous layer was extracted 2x more with CH_2Cl_2 and the combined organic phases were washed with $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue (1.31 g) was distilled (bp 45–47 °C, (0.1 mm)) to give 1.16 g of **4a** (81%) as a clear oil; IR, 3600, 1700 cm^{-1}; ^1H NMR δ 4.04 (1 H, m), 3.15 (1 H, d, exchanges w/D_2O), 2.63 (1 H, dd, J = 17, 3 Hz), 2.53 (1 H, dd, J = 17, 9 Hz), 2.21 (3 H, s), 1.5–1.2 (6 H, m), 0.91 (3 H, t); MS calcd for $C_8H_{14}O$, m/e 126.1045, found m/e 126.1045.

4-Hydroxy-4-phenyl-2-butanone (4b). **4b** was made by reduction of 3-methyl-5-phenyl-Δ^2-isoxazoline[8] (118 mg, 0.73 mol) according to method 1 (167 μL, 1.46 mmol of $B(OCH_3)_3$ as buffer): yield 99 mg (83%) after recrystallization (CCl_4, −20 °C); mp 35–36 °C (lit. 34–36 °C[43]); IR 3600, 1705 cm^{-1}; ^1H NMR δ 7.3–7.2 (5 H, m), 5.13 (1 H, br, d), 3.38 (1 H, br, s, exchanges with D_2O), 2.88 (1 H, dd, J = 17.5, 8.7 Hz), 2.75 (1 H, dd, J = 17.5, 4.3 Hz), 2.18 (3 H, s).

3-Phenyl-5-*n*-butyl-Δ^2-isoxazoline (3c) (Method B[7]). A solution of Et_3N (1.53 mL, 11 mmol) in dry ether (10 mL) was added dropwise to phenylhydroximic acid chloride[44] (1.55 g, 10 mmol) in ether (10 mL) and 1-hexene (1.68 g, 20 mmol) at −20 °C. The reaction was allowed to warm slowly to room temperature and stirred 12 h. Filtration, followed by concentration of the filtrate in vacuo, gave the crude product that was recrystallized from MeOH/H_2O to give 1.39 g (74%) **3c**[45] as a white solid (mp 40.5–41 °C): ^1H NMR (90 MHz) δ 7.7–7.1 (5 H, m), 4.66 (1 H, m), 3.33 (1 H, dd), 2.85 (1 H, dd), 1.7–0.8 (9 H, m).

3-Hydroxy-1-phenyl-1-heptanone (4c) (Method 2, General Raney-Nickel/Boric Acid Reduction Procedure). To a solution of isoxazoline **3c** (351 mg, 1.8 mmol) in 5/1 methanol/water (10 mL) was added boric acid (227 mg, 3.7 mmol) and a spatula tip (estimated 10–20 mg) of W-2 Raney nickel. The reaction was placed under hydrogen by repeated (~5 times) evacuation and flushing with H_2 gas by means of a balloon attached to a three-way stopcock. The mixture was stirred vigorously for 2.5 h and then filtered through Celite into a separatory funnel containing water and CH_2Cl_2. After separation, the aqueous layer was extracted with CH_2Cl_2 2 more times and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo to yield 345 mg (98%) of crude hydroxy ketone. Distillation (0.4 mm, Kugel-Rohr, 85 °C) gave 246 mg of **4c** as a clear oil: IR 3550, 1687 cm^{-1}; ^1H NMR δ 7.96 (2 H, dd), 7.59 (1 H, dt), 7.47 (2 H, t), 4.22 (1 H, m), 3.25 (1 H, br, s), 3.17 (1 H, dd, J = 17, 2.8 Hz), 3.04 (1 H, dd, J = 17, 8.9 Hz), 1.7–1.0 (6 H, m), 0.92 (3 H, t). Anal ($C_{13}H_{18}O_2$) C, H.

Isoxazoline 3d was prepared according to method A with methylene cyclopentane (1 g, 12 mmol), PhNCO (2.7 mL, 26 mmol), 1-nitropropane (1.1 mL, 13 mmol), and Et_3N (50 μL) in PhH (30 mL). After 14 h at 23 °C and 1 h reflux, 2.01 g of adduct **3d** was isolated admixed with ~25% furoxane dimer. Distillation (bp 58–60 °C (0.8 mm)) did not effect separation nor did flash chromatography (8/1 hexane/EtOAc) and the product was reduced as the mixture: ^1H NMR δ 2.84 (2 H, s), 2.45 (2 H, q), 2.1–1.5 (8 H, m), 1.18 (3 H, t).

β-Hydroxy Ketone 4d. Reduction by method 2 was carried out with isoxazoline **3d** (131 mg, contains ~25% dimer) and $B(OH)_3$ (264 mg, 2 mmol) for 7 h at 23 °C. After distillation (75 °C, Kugel-Rohr, 0.7 mm) 95 mg (>90%) **4d** was obtained as a clear oil: IR, 3500, 1699, cm^{-1}; ^1H NMR δ 3.62 (1 H, s), 2.74 (2 H, s), 2.46 (2 H, q), 1.9–1.4 (8 H, m), 1.07 (3 H, t). Anal ($C_9H_{16}O_2$) C, H.

3,5-Dimethyl-5-*n*-propyl-Δ^2-isoxazoline (3e) was prepared by method A with nitroethane (1.1 mL, 15 mmol), phenyl isocyanate (3.3 mL, 30 mmol), 2-methyl-1-pentene (3.7 mL, 30 mmol), and triethylamine (50 μL) in benzene (24 mL). After distillation (25 °C, Kugel-Rohr, 0.1 mm) 1.40 g (66%) of **3e** was obtained as a nearly clear oil: ^1H NMR δ 2.73 (1 H, dq, J = 17, 1 Hz), 2.60 (1 H, dq, J = 17, 1 Hz), 1.96 (3 H, t, J = 1 Hz), 1.62 (2 H, m), 1.46 (2 H, m), 0.95 (3 H, t). Anal ($C_8H_{15}NO$) C, H.

4-Hydroxy-4-methyl-2-heptanone (4e). Reduction was performed according to method 1 with **3e** (141 mg, 1 mmol), $B(OCH_3)_3$ (125 μL, 2 mmol) in 15/1 MeOH/H_2O (4 mL). After 14 h, yield 133 mg. Pu-

(42) Mozingo, R. "Organic Synthesis"; Wiley: New York, 1955; Collect. Vol. III, p 181.

(43) Noyce, D. S.; Reed, W. L. *J. Am. Chem. Soc.* **1958**, *80*, 5539.
(44) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.
(45) Bianchi, G.; Grünanger, P. *Tetrahedron* **1965**, *21*, 817.

rified by distillation (40 °C, Kugel-Rohr, 0.2 mm) to give 121 mg (84%) of **4e** as a clear oil: IR 3500, 1700 cm^{-1}; ^1H NMR δ 3.74 (1 H, s), 2.64 (1 H, d), 2.57 (1 H, d), 2.19 (3 H, s), 1.5–1.2 (4 H, m), 1.20 (3 H, s), 0.94 (3 H, t). Anal ($C_8H_{16}O_2$) C, H.

Norcamphor adduct 3f was prepared according to method A with the olefin[21] (216 mg, 2 mmol), PhNCO (480 μL, 2.2 mmol), nitroethane (158 μL, 1.1 mmol), and Et_3N (50 μL) in benzene (15 mL, 48 h, 23 °C). Adduct **3f** (152 mg, 46%) was obtained as a faint yellow oil: bp 80 °C (Kugel-Rohr, 0.8 mm); ^1H NMR δ 4.01 (1 H, d, J = 16 Hz), 3.72 (1 H, d, J = 16 Hz), 2.5–1.0 (10 H, m), 1.98 (3 H, s). Anal ($C_{10}H_{15}NO$) C, H.

Exo hydroxy compound 4f. Reduction was by method 2 with isoxazoline **3f** (51 mg, 0.31 mmol), $B(OH)_3$ (82 mg, 1.2 mmol), 90 min, 23 °C. Adduct **4f** (41 mg, 79%) was obtained after distillation (70 °C, Kugel-Rohr, 0.5 mm): IR 3500, 1698 cm^{-1}; ^1H NMR δ 3.53 (1 H, s), 2.82 (1 H, d, J = 18 Hz), 2.77 (1 H, d, J = 18 Hz), 2.4–1.0 (10 H, m), 2.19 (3 H, s). Anal ($C_{10}H_{16}O_2$) C, H.

Endo Hydroxy Adduct 7. To a solution of norcamphor (330 mg, 3 mmol) in dry THF (6 mL) at −78 °C was added allylmagnesium bromide (1 M in Et_2O, 4 mL, 4 mmol) dropwise via syringe. After 4 **h** at −78 °C the reaction was warmed to 23 °C and poured into ammonium chloride solution. Standard workup gave 439 mg (96%) of a single alcohol. The crude alcohol (152 mg, 1 mmol), $PdCl_2$ (35 mg, 0.2 mmol), and CuCl (100 mg, 1 mmol) were stirred under O_2 in dry DMF (1 mL) for 14 h at 23 °C. The reaction mixture was poured into water and extracted with ether. The organic layer was washed with H_2O (3x) and brine, dried over $MgSO_4$, and concentrated in vacuo to give 154 mg of a mixture of products. Separation by flash chromatography (18% EtOAc in hexanes) gave 101 mg of a less polar fraction isomeric with starting material (MS, m/e 152 (M^+); IR no carbonyl) and 59 mg (35%) of a more polar fraction identified as adduct **7**: IR 3500, 1710 cm^{-1}; ^1H NMR 3.77 (1 H, s), 2.74 (2 H, s), 2.17 (3 H, s), 2.2–1.2 (10 H, m).

***trans*-3,4,5-Trimethyl-Δ^2-isoxazoline (8t).** Method A was employed with excess *trans*-2-butene (solvent), 0–23 °C. The product was distilled at aspirator pressure: bp 62–65 °C; ^1H NMR δ 4.14 (1 H, dq), 2.72 (1 H, m), 1.94 (3 H, s), 1.36 (3 H, d), 1.19 (3 H, d); MS calcd for $C_6H_{11}NO$, m/e 113,0841; found, m/e 113.0842.

***cis*-3,4,5-Trimethyl-Δ^2-isoxazoline (8c)** was prepared by method A, as above with *cis*-2-butene: bp 67–76 °C (aspirator). The product contained a small amount of trans adduct presumably arising from faster cycloaddition with trace amounts of *trans*-2-butene impurity; ^1H NMR δ 4.60 (1 H, m), 3.02 (1 H, m), 1.95 (3 H, s), 1.27 (3 H, d), 1.07 (3 H, d); MS calcd for $C_6H_{11}NO$, m/e 113.0841; found, m/e 113.0841.

(*R*,S)-4-Hydroxy-3-methyl-2-pentanone (9e).**[46] Reduction was performed by method 1 with isoxazoline **8c** (113 mg, 1 mmol) and $B(OCH_3)_3$ (227 μL, 2 mmol): Yield 89 mg (77%) after distillation as a clear oil (45 °C, Kugel-Rohr, 0.1 mm); IR 3500, 1700 cm^{-1}; ^1H NMR δ 4.10 (1 H, m), 2.65 (1 H, br, s), 2.51 (1 H, m), 2.17 (3 H, s), 1.12 (6 H, 2 overlapping d), decoupling showed $J_{3,4}$ = 3.6 Hz.

(*R*,R)-4-Hydroxy-3-methyl-2-pentanone (9t).**[46] Reduction was carried out as above with **8t** to give 96 mg (83%) of **9t** as a clear oil after distillation (45 °C, Kugel-Rohr, 0.1 mm): IR 3500, 1702 cm^{-1}; ^1H NMR δ 3.92 (1 H, m), 2.70 (1 H, br, s), 2.57 (1 H, m), 2.20 (3 H, s), 1.21 (3 H, d), 1.12 (3 H, d), decoupling showed $J_{3,4}$ = 7.7 Hz.

3-Methyl-*trans*-4,5-diprop-1-yl-Δ^2-isoxazoline (10t) was prepared via method A with nitroethane (370 μL, 5 mmol), PhNCO (1.1 mL, 10 mmol), *trans*-4-octene (1.6 mL, 10 mmol), and Et_3N (50 μL). After distillation (bp 71–72 °C (0.08 mm)), isoxazoline **10t** (391 mg) was obtained as a clear oil: ^1H NMR δ 4.20 (1 H, m), 2.71 (1 H, m), 1.93 (3 H, narrow d), 1.7–1.2 (8 H, m), 0.95 (6 H, 2 overlapping t); MS calcd for $C_{10}H_{19}NO$, m/e 169.1467; found, m/e 169.1465.

(*R*,R)-4-Hydroxy-3-prop-1-yl-2-heptanone (11t).** Reduction was performed by method 1 with isoxazoline **10t** (100 mg, 0.59 mmol) and $B(OCH_3)_3$ (134 μL, 1.2 mmol). The crude product (103 mg) was recrystallized from hexane (−25 °C) to give **11t** (80 mg, 79%) as a white solid: mp 39.5–40 °C; IR 3500, 1700 cm^{-1}; ^1H NMR δ 3.71 (1 H, m), 2.60 (1 H, m), 2.45 (1 H, d, exchanges with D_2O), 2.20 (3 H, s), 1.7–1.2 (8 H, m), 0.94 (6 H, 2 overlapping t), decoupling showed $J_{3,4}$ = 5.9 Hz; MS calcd for $C_{10}H_{18}O$ ($M - H_2O$), m/e 154.1358; found, m/e 154.1358. Anal ($C_{10}H_{20}O_2$) C, H.

3-Phenyl-*trans*-4,5-dimethyl-Δ^2-isoxazoline (12t)[10] was prepared by method B: ^1H NMR δ 7.68 (2 H, m), 7.41 (3 H, m), 4.45 (1 H, m), 3.31 (1 H, m), 1.38 (3 H, d), 1.30 (3 H, m).

3-Phenyl-*cis*-4,5-dimethyl-Δ^2-isoxazoline (12c)[10] was prepared by method B: ^1H NMR δ 7.72 (2 H, m), 7.42 (3 H, m), 4.70 (1 H, m), 3.49 (1 H, m), 1.46 (3 H, d), 1.14 (3 H, d).

(*R*,R)-3-Hydroxy-2-methyl-1-phenyl-1-butanone (13t).** Method 2 was employed with **12t** (278 mg, 1.6 mmol) and boric acid (493 mg, 8.0 mmol) to give threo product **13t** (269 mg, 97%). Distillation (80 °C, Kugel-Rohr, 0.7 mm) gave 192 mg (70%) of product as a clear oil: IR 3500, 1685 cm^{-1}; ^1H NMR δ 7.97 (2 H, m), 7.60 (1 H, t), 7.47 (2 H, t), 4.12 (1 H, m), 3.48 (1 H, m), 2.85 (1 H, br, s), 1.29 (3 H, d), 1.24 (3 H, d), decoupling showed $J_{1,2}$ = 6.7 Hz; MS calcd for $C_{11}H_{12}O$ ($M = H_2O$), m/e 160.0888; found, m/e 160,0888. Anal ($C_{11}H_{14}O_2$) C, H.

(*R*,S)-3-Hydroxy-2-methyl-1-phenyl-1-butanone (13e).** Method 2 was employed with **12c** (242 mg, 1.39 mmol) and boric acid (430 mg, 6.9 mmol) to give erythro product **13e** (219 mg, 90%). Distillation (75 °C, Kugel-Rohr, 0.7 mm) gave 178 mg (73%) of product as a clear oil: IR 3500, 1685 cm^{-1}; ^1H NMR δ 7.96 (2 H, m), 7.60 (1 H, t), 7.48 (2 H, t), 4.11 (1 H, dq), 3.49 (1 H, dq), 3.13 (1 H, br, s), 1.29 (3 H, d), 1.24 (3 H, d); MS calcd for $C_{11}H_{12}O$ ($M - H_2O$), m/e 160.0888; found, m/e 160.0888. Anal ($C_{11}H_{14}O_2$) C, H.

***cis*-2-(1-Oxoethyl)cyclopentanol (17e).** Reduction was achieved by using method B with isoxazoline **16c** (11 mg) and boric acid (22 mg). The crude product **17e** was isolated as a clear oil: IR 3500, 1695 cm^{-1}; ^1H NMR δ 4.50 (1 H, m), 3.13 (1 H, br, d), 2.88 (1 H, m), 2.23 (3 H, s), 2.1–1.6 (6 H, m).

***cis*-2-(1-Oxoethyl)cyclohexanol (15e).** Method 1 was employed for reduction with isoxazoline **14c** (43 mg, 0.31 mmol) and $B(OCH_3)_3$ (70 μL, 0.62 mmol). The crude product was recrystallized from hexane (−20 °C) to give **15e** (38.3 mg, 87%) as a white solid: mp 38–40 °C; IR 3550, 1700 cm^{-1}; ^1H NMR δ 4.22 (1 H, br), 3.2 (1 H, br, s), 2.50 (1 H, m), 2.19 (3 H, s), 2.0–1.2 (8 H, m); MS calcd for $C_8H_{14}O_2$, m/e 142.0994; found, m/e 142.0994.

3-Phenyl-5-hydroxymethyl-Δ^2-isoxazoline Tetrahydropyranyl Ether (18c). To a solution of isoxazoline **18a**[47] (354 mg, 2 mmol) and dihydropyran (364 μL, 3 mmol) in dry CH_2Cl_2 (10 mL) was added a small crystal of PPTS.[48] After the solution was stirred 18 h at 23 °C, the reaction was washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified to flash chromatography (SiO_2, 20% EtOAc/hexane) to give 525 mg of **18c** (100%) as a clear oil: ^1H NMR δ 7.60 (2 H, m), 7.32 (3 H, m), 4.95 (1 H, m), 4.67 (1 H, br), 4.0–3.1 (6 H, m), 1.9–1.5 (6 H, m); MS calcd for $C_{15}H_{19}NO_3$, m/e 261.1364; found, m/e 261.1364.

3-Phenyl-5-hydroxymethyl-Δ^2-isoxazoline *tert*-Butyldimethylsilyl Ether (18b). A solution of isoxazoline **18a**[47] (354 mg, 2 mmol), *tert*-butyldimethylchlorosilane (350 mg, 2.3 mmol), imidazole (240 mg), and dry DMF (2 mL) was stirred for 18 h at 23 °C. The reaction was diluted with ether, washed with water (3x) and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified as above to give 545 mg (94%) of silyl ether **18b** as a clear oil: ^1H NMR δ 7.58 (2 H, m), 7.38 (3 H, m), 4.81 (1 H, m), 3.77 (1 H, dd), 3.73 (1 H, dd), 3.35 (1 H, dd), 3.28 (1 H, dd), 0.88 (9 H, s), 0.09 (3 H, s), 0.06 (3 H, s); MS calcd for $C_{12}H_{16}O_2Si$ ($M - t$-Bu), m/e 234.0950; found, m/e 234.0950.

3,4-Dihydroxy-1-phenyl-1-butanone (19a). Reduction was performed by method 2 on **18a** using the usual 0.25 mmol scale to give 32 mg of diol **19a** as a white solid (mp 69.7–70.7) after flash chromatography (33% EtOAc/hexane): IR 3600, 3500, 1675 cm^{-1}; ^1H NMR δ 7.97 (2 H, d), 7.61 (1 H, t), 7.49 (2 H, t), 4.36 (1 H, br), 3.78 (1 H, m), 3.65 (1 H, m), 3.51 (1 H, br, s), 3.22 (2 H, m), 2.15 (1 H, br, t); MS calcd $C_{10}H_{10}O_2$ ($M - H_2O$), m/e 162.0681; found, m/e 162.0683. Anal ($C_{10}H_{12}O_3$) C, H.

THP Ether 19c. Isoxazoline **18c** was reduced as above to give 55 mg (84%) of **19c** as a white solid (mp 71–81 °C) after flash chromatography (34% EtOAc/hexane); IR 3500, 1675 cm^{-1}; ^1H NMR δ 7.99 (2 H, d), 7.58 (1 H, t), 7.48 (2 H, t), 4.52 (1 H, m), 4.45 (1 H, br), 4.0–3.4 (5 H, m), 4.22 (2 H, m), 2.0–1.5 (6 H, m); MS calcd for $C_{15}H_{20}O_4$, m/e 264.1362; found, m/e 262.1384.

***tert*-Butyldimethylsilyl Ether 19b.** Isoxazoline **18b** was reduced as above to give 61 mg (83%) of **19b** as a clear oil after flash chromatography (17% EtOAc/hexane): IR 3500, 1685 cm^{-1}; ^1H NMR δ 7.97 (2 H, d), 7.59 (1 H, t), 7.47 (2 H, t), 4.29 (1 H, m), 3.69 (2 H, m), 3.15 (3 H, m), 0.92 (9 H, s), 0.09 (3 H, s), 0.08 (3 H, s); MS calcd for $C_{12}H_{17}O_3$ ($M - t$-bu), m/e 237.0947; found, m/e 237.0947.

***trans*-5-*n*-Butyl-4-methyl-3-phenyl-Δ^2-isoxazoline (23a).** This was prepared following the procedure of Jäger.[34] Isoxazoline **3c** (203 mg, 1 mmol) in dry THF (1 mL) was added dropwise to a solution of lithium diisopropylamide (1.05 mmol) in THF (3 mL) containing HMPA (350 μL, 2 mmol) at −78 °C. After the deep red reaction was maintained at −78 °C for 1 h, methyl iodide (267 μL, 4 mmol) was added rapidly via syringe. After warming, the reaction was poured into dilute NH_4Cl and extracted with Et_2O. The organic phase was washed with $NaHSO_4$, water (4x), and brine, dried over $MgSO_4$, and concentrated in vacuo.

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(47) Quilico, A.; Stagno D'Alcontres, G.; Grünanger, P. *Nature (London)* **1950**, *166*, 226.

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The residue was purified by flash chromatography (10% EtOAc/hexane) to give 185 mg (85%) of **23a** as a clear oil that was 12.5/1 trans/cis as evidenced by 300-MHz NMR: ^{1}H NMR (major) 7.68 (2 H, m), 7.40 (3 H, m), 4.33 (1 H, m), 3.35 (1 H, dq), 1.8–1.2 (6 H, m), 1.30 (3 H, d), 0.93 (3 H, t). Anal ($C_{14}H_{19}NO$) C, H.

(*R*,R)-3-Hydroxy-2-methyl-1-phenyl-1-heptanone (24a).** Reduction was performed by method 2 with isoxazoline **23a** (40 mg, 0.18 mmol) and boric acid (50 mg, 0.8 mmol), 2 h, 23 °C. After distillation (65 °C, Kugel-Rohr, 0.05 mm) 37 mg (91%) of **24a** was isolated as a clear oil: IR 3500, 1680 cm^{-1}; ^{1}H NMR δ 7.95 (2 H, d), 7.60 (1 H, t), 7.48 (2 H, t), 3.87 (1 H, m), 3.55 (1 H, m), 2.86 (1 H, br, s), 1.5–1.2 (6 H, m), 1.28 (3 H, d), 0.90 (3 H, t). Anal ($C_{14}H_{20}O_2$) C, H.

***trans*-5-*n*-Butyl-4-ethyl-3-phenyl-Δ^2-isoxazoline (23b).** Isoxazoline **3c** (150 mg, 0.74 mmol) was alkylated with iodoethane as above, and the product was purified by flash chromatography (5% EtOAc/hexane) to give 131 mg (77%) of **23b**: ^{1}H NMR δ 7.59 (2 H, m), 7.40 (3 H, m), 4.45 (1 H, m), 3.26 (1 H, m), 1.8–1.2 (8 H, m), 0.93 (6 H, 2 overlapping t). Anal ($C_{15}H_{21}NO$) C, H.

(*R*,R)-2-Ethyl-3-hydroxy-1-phenyl-1-heptanone (24b).** Reduced by method 2 with isoxazoline **23b** (18 mg, 0.08 mmol) and boric acid (50 mg, 0.8 mmol). The product was distilled (80 °C, Kugel-Rohr, 0.01 mm) to give 15.1 mg (83%) of **24b** as a clear oil: IR 3550, 1680 cm^{-1}; ^{1}H NMR δ 7.96 (2 H, d), 7.60 (1 H, t), 7.49 (2 H, t), 3.88 (1 H, m), 3.56 (1 H, m), 1.9–1.2 (8 H, m), 0.95 (3 H, t), 0.86 (3 H, t). Anal ($C_{19}H_{22}O_2$) C, H.

Isoxazoline 28. To a mixture of 1-phenylprop-2-en-1-ol *tert*-butyldimethylsilyl ether (228 mg, 0.1 mmol), Et_3N (30 μL, 0.2 mmol), CH_2Cl_2 (4 mL), and 5% NaOCl (2 mL) was added benzaldoxime (180 mg, 1.5 mmol) in CH_2Cl_2 (2 mL).[49] After 2 h at 0 °C the organic phase was separated, washed with water and brine, dried over Na_2SO_4, and concentrated in vacuo. ^{1}H NMR analysis of the crude product revealed a 77/23 mixture of diastereomers that were not separable by TLC. Pure samples of each diastereomer were obtained by shaving on the HPLC (3% EtOAc/hex): ^{1}H NMR (major) (**28**) δ 7.66 (2 H, m), 7.40 (8 H, m), 5.09 (1 H, d, J = 3 Hz), 4.83 (1 H, m), 3.49 (1 H, dd, J = 16, 7.5 Hz), 3.03 (1 H, dd, J = 16, 10 Hz), 0.85 (9 H, s), 0.10 (3 H, s), –0.03 (3 H, s); MS calcd for $C_{18}H_{20}NO_2Si$ (M – t-Bu), m/e 310.1263; found, m/e 310.1263.

Isoxazoline 29. Major diastereomer **28** (32 mg, 0.1 mmol) was alkylated as above with iodomethane. The product was purified by preparative TLC (SiO_2, 3% EtOAc/hexane) to give 22 mg (66%) of **29** as a clear oil: ^{1}H NMR δ 7.56 (2 H, m), 7.40 (8 H, m), 4.96 (1 H, d, J = 3.0 Hz), 4.37 (1 H, dd, J = 3, 5.4 Hz), 3.88 (1 H, dq, $J \approx$ 5.4, 7.0 Hz), 1.01 (3 H, d, J = 7 Hz), 0.85 (9 H, s), 0.05 (3 H, s), –0.88 (3 H, s).

Hydroxy Ketone 30. Isoxazoline **29** (10 mg) was reduced by method 2. After preparative TLC (SiO_2, 3% EtOAc/hexanes, 2 passes) 4.4 mg (44%) of **30** was isolated as a clear oil; IR 3500, 1685 cm^{-1}, ^{1}H NMR δ 7.91 (2 H, d), 7.60 (1 H, t), 7.49 (2 H, t), 7.3 (5 H, m), 4.91 (1 H, d, J = 3.8 Hz), 4.68 (1 H, d, J = 9.1 Hz), 3.89 (1 H, dt, $J \approx$ 9.1, 3.8 Hz), 3.55 (1 H, dq, J = 3.0, 7.3 Hz), 1.27 (3 H, d, J = 7.3 Hz), 0.72 (9 H, s), –0.10 (3 H, s), –0.26 (3 H, s); MS calcd for $C_{19}H_{23}O_3Si$ (M – t-Bu), m/e 327.1416; found, m/e 327.1413.

(*E*)- and (*Z*)-1-Nitro-6-octene. To a suspension of pyridinium chlorochromate (26.45 g, 0.3 mol) in dry CH_2Cl_2 (100 mL) was added 6-chloro-1-hexanol (11.3 mL, 0.1 mol) in CH_2Cl_2 (50 mL). After the mixture was stirred 14 h (23 °C), Et_2O (400 mL) was added followed by Florisil, until a granular solid was formed. The mixture was filtered through a short bed of Florisil eluting with ether and concentrated in vacuo to give 10.31 g of 6-chlorohexanal.

To a suspension of ethyltriphenylphosphonium bromide (8.90 g, 24 mmol) in dry THF (20 mL) was added potassium *tert*-butoxide (2.46 g, 22 mmol) in THF (20 mL). After the orange mixture was stirred 15 min at 23 °C, the reaction was cooled to –78 °C and 6-chlorohexanal (2.67 g, 20 mmol) was added dropwise in THF (5 mL). After it was stirred 2 h at –78 °C and 14 h at 23 °C, the reaction was poured into water and extracted with pentane (3x). The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was passed through a short Florisil column eluting with pentane, and the pentane was concentrated in vacuo to give 1-chloro-6-octene (2.14 g) as an undetermined isomeric mixture (largely cis): ^{1}H NMR δ 5.4 (2 H, m), 3.53 (2 H, t), 2.2–1.2 (11 H, m).

A mixture of the above chloro olefin (2.14 g, 14.6 mmol), sodium iodide (9 g, 60 mmol), and acetone (50 mL) was heated at reflux for 12 h. After dilution with water, the mixture was extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was passed through a short Florisil column eluting with pentane to give 1-iodo-6-octene (3.01 g) as a clear oil: ^{1}H NMR δ 3.19 (2 H, t).

To a solution of above iodide (2.91 g, 12.2 mmol) in dry DMF (25 mL) was added $NaNO_2$ (1.35 g, 19.5 mmol).[50] After it was stirred 3.5 h at 23 °C, the mixture was poured into water and extracted with ether. The organic layer was washed with water (3x) and brine, dried over $MgSO_4$, and concentrated in vacuo. ^{1}H NMR analysis indicated significant olefin isomerization. (Possibly via iodine formation?) Flash chromatography of the residue (6% EtOAc/hexane) gave nitrite ester (385 mg, less polar) and 1-nitro-6-octene (911 mg, more polar) as a 3/2 mixture of trans/cis isomers: IR 1560, 1390 cm^{-1}; ^{1}H NMR 5.42 (2 H, m), 4.38 (2 H, 2 close t), 2.01 (4 H, m), 1.74 (3 H, 2 br, d), 1.50 (4 H, m); MS, m/e 157 (M$^+$), 140, 109, 55.

Isoxazolines 31a and 33a were prepared by method A with 1-nitro-6-octene (3/2 trans/cis, 850 mg, 7.1 mmol), PhNCO (1.23 mL, 14.9 mmol), and Et_3N (140 μL). After 36 h at 23 °C, the product was purified by flash chromatography (12% EtOAc/hexane) to give the less polar threo isomer **31a**: bp 50 °C (Kugel-Rohr, 0.1 mm), mp 22–25 °C; ^{1}H NMR δ 4.16 (1 H, dq), 2.70 (2 H, m), 2.2–1.2 (7 H, m), 1.51 (3 H, d). MS calcd for $C_8H_{13}NO$, m/e 139.0997; found, m/e 139.0998; and more polar erythro isomer **33a**: bp 40 °C, (Kugel-Rohr, 0.1 mm); ^{1}H NMR δ 4.71 (1 H, dq), 3.05 (1 H, m), 2.76 (1 H, br, d), 2.2–1.3 (7 H, m), 1.21 (3 H, d); MS calcd for $C_8H_{13}NO$, m/e 139.0997; found, m/e 139.0998.

1-Nitro-5-heptene (Mixture of *E* and *Z* Isomers). This was prepared from 5-chloropentanal as above: IR 1560, 1395 cm^{-1}; ^{1}H NMR dd 5.40 (2 H, m), 4.36 (2 H, 2 close t), 2.2–1.3 (9 H, m); MS, m/e 143 (M$^+$), 95, 82, 81, 55.

Isoxazolines 31c and 33c were prepared by method A with 1-nitro-5-heptene (2/1, cis/trans; 570 mg, 4 mmol), PhNCO (910 μL, 8.4 mmol), and Et_3N (140 μL). After 14 h at 23 °C, the product was purified by flash chromatography (12% EtOAc/hexane) to give the less polar threo isomer **31c**: ^{1}H NMR δ 4.33 (1 H, m), 3.28 (1 H, br, q), 2.4–1.9 (8 H, m), 1.48 (3 H, d); MS (of mixture) calcd for $C_7H_{11}NO$, m/e 125.0841; found, m/e 125.0841. The more polar erythro isomer **33c**: bp 95 °C (Kugel-Rohr, aspirator pressure); ^{1}H NMR δ 4.77 (1 H, m), 3.76 (1 H, br, q), 2.5–1.5 (8 H, m), 1.12 (3 H, d). Anal ($C_7H_{11}NO$) C, H.

1-Nitro-7-phenyl-6-heptene (Mixture of *E* and *Z* Isomers). To a suspension of benzyltriphenylphosphonium bromide (9.54 g, 24 mmol) in dry THF (30 mL) was added *n*-BuLi (1.5 M in hexane, 16.4 mL, 24 mmol) dropwise via syringe at 0 °C. The deep red solution was allowed to warm to 23 °C and stirred 15 min at which time 6-chlorohexanal (3.0 g, 22 mmol) in THF (10 mL) was added dropwise. After 14 h at 23 °C, the reaction was poured into water and extracted with pentane. The organic phase was washed with water and brine and dried over Na_2SO_4. After concentration in vacuo, the residue was filtered through silica gel to give 3.04 g of olefin as a clear oil (2/1, trans/cis); ^{1}H NMR δ 6.42 (1 H, d, J = 16 Hz, trans), 6.46 (1 H, d, J = 12 Hz, cis).

Iodide and nitro formation were performed as above to give 1-nitro-7-phenyl-6-heptene (2/1, trans/cis): IR 1590, 1550, 1390; ^{1}H NMR δ 7.4–7.1 (5 H, m), 6.4 (1 H, 2 overlapping d), 6.19 (1 H, dt, trans), 5.63 (1 H, dt, cis), 4.37 (2 H, 2 overlapping t), 2.6–1.5 (8 H, m); MS calcd for $C_{13}H_{17}NO_2$, m/e 219.1259; found, m/e 219.1259.

Isoxazolines 31b and 33b. Prepared by method A (48 h, 23 °C), the isomers were separated by preparative HPLC to give the less polar threo isomer **31b**: bp 90 °C (0.1 mm, Kugel-Rohr), mp 64–65 °C (hexane/$CHCl_3$); ^{1}H NMR δ 7.35 (5 H, m), 5.04 (1 H, d, J = 9.9 Hz), 3.02 (1 H, m), 2.81 (1 H, br, d), 2.4–1.3 (7 H, m); MS calcd for $C_{13}H_{15}NO$, m/e 201.1154; found, m/e 201.1154. Anal ($C_{13}H_{15}NO$) C, H. The more polar erythro isomer **33b**: mp 109–110 °C (hexane/Et_2O/$CHCl_3$); ^{1}H NMR δ 7.4–7.2 (5 H, m), 5.66 (1 H, d), 3.37 (1 H, m), 2.84 (1 H, br, d), 2.3–0.7 (7 H, m); MS calcd for $C_{13}H_{15}NO$, m/e 201.1154; found, m/e 201.1156. Anal ($C_{13}H_{15}NO$) C, H.

Threo Adduct 32a. Reduction was by method 2 with isoxazoline **31a** (35 mg, 0.25 mmol) and boric acid (62 mg, 1 mmol, 2 h, 23 °C) to give **32a**[51] (30.5 mg, 85%) as a clear oil: bp 60 °C (Kugel-Rohr, 0.1 mm); IR 3550, 1690 cm^{-1}; ^{1}H NMR 3.94 (1 H, m), 3.77 (1 H, br, s), 2.5–1.3 (8 H, m), 1.16 (3 H, d), decoupling shows J_{threo} = 7.7 Hz; MS, m/e 143, 142 (M$^+$), 124 (M – H_2O), calcd $C_8H_{12}O$, m/e 124.0888; found, m/e 124.0888.

Erythro Adduct 34a. Method 2 was employed for reduction on scale as above with isoxazoline **33a** to give **34a**[51] (32 mg, 90%) as a clear oil:

(49) Lee, G. A. *Synthesis* **1982**, 508.

(50) Kornblum, N. *Org. React.* (*N.Y*) **1966**, *12*, 101.

(51) Dubois, J.-E.; Dubois, M. *Bull.* Chim. *Soc. Fr.* **1969**, 3126; **1969**, 3553.

bp 60 °C (Kugel-Rohr, 0.1 mm); IR 3550, 1695; ^{1}H NMR δ 4.27 (1 H, m), 2.80 (1 H, br, s), 2.5–1.5 (8 H, m), 1.15 (3 H, d), decoupling shows $J_{erythro}$ = 3.0 Hz; MS calcd for $C_8H_{12}O$ (M − H_2O), *m/e* 124.0888; found, *m/e* 124.0888.

Threo Adduct 32c. Reduction was carried out by method 2 on scale as above with isoxazoline **31c** to give **32c**[51] (32.5 mg, 84%): IR 3500, 1720 cm^{-1}; ^{1}H NMR δ 4.20 (1 H, br, s), 3.83 (1 H, m), 2.5–1.4 (7 H, m), 1.18 (3 H, d), decoupling shows J_{threo} = 8.5 Hz; MS, *m/e* 110 (M − H_2O), 84.

Erythro Adduct 34c. Reduction was performed method 2 on scale as above with isoxazoline **33c** to give **34c**[51] (33.3 mg, 86%): IR 3500, 1720 cm^{-1}; ^{1}H NMR δ 4.27 (1 H, br), 2.4–1.8 (7 H, m), 1.23 (3 H, d), decoupling shows $J_{erythro}$ = 2.6 Hz; MS calcd for $C_7H_{10}O$ (M − H_2O), *m/e* 110.0732; found, *m/e* 110.0732.

Threo Adduct 32b. Reduction was by method 2 with isoxazoline **31b** on scale as above to give **32b** (36.5 mg, 73%) as a white powder after recrystallization from hexane/Et_2O: mp 71–73 °C, lit. mp 74–75 °C[52]; IR 3500, 1690 cm^{-1}; ^{1}H NMR δ 7.3 (5 H, m), 4.79 (1 H, dd, *J* = 8.7, 2 Hz), 3.96 (1 H, d, *J* = 2 Hz, exchanges with D_2O), 2.7–1.2 (9 H, m); MS calcd for $C_{13}H_{16}O_2$, *m/e* 204.1150; found, *m/e* 204.1150.

Erythro Adduct 34b. Reduction was carried out by method 2 with isoxazoline **33b** on scale as above to give **34b** (37.5 mg, 74%) as white needles after recrystallization from Et_2O/hexane: mp 101.5–102.5, lit. mp 102–103 °C;[52] IR 3550, 1695 cm^{-1}; ^{1}H NMR δ 5.40 (1 H, narrow t, *J* = 2.2 Hz), 3.03 (1 H, d, *J* = 2 Hz, exchanges with D_2O), 2.6–1.5 (9 H, m); MS calcd for $C_{13}H_{16}O_2$, *m/e* 204.1150; found, *m/e* 204.1150.

(*E*)-Ethyl 7-Chloro-2-methyl-2-octenoate. To a suspension of oil-free NaH (50% in oil, 528 mg, 11 mmol) in dry DME (5 mL) was added triethyl 2-phosphonopropionate (2.62 g, 11 mmol) in DME (20 mL) dropwise via syringe (H_2 evolution).[53] The mixture was stirred 90 min at 23 °C and then 6-chlorohexanal (1.34 g, 10 mmol) was introduced in DME (4 mL). After 4 h at 23 °C the reaction was heated to 50 °C for 16 h, cooled, poured into H_2O, and extracted with ether. The organic phase was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 10% EtOAc/hexane) to give 1.4 g of chloro olefin: IR 1700, 1650 cm^{-1}; ^{1}H NMR δ 6.74 (1 H, br, t), 4.19 (2 H, q), 3.54 (2 H, t), 2.3–1.4 (8 H, m), 1.83 (3 H, br), 1.27 (3 H, t); MS calcd for $C_{11}H_{19}ClO_2$, *m/e* 218.1074; found, *m/e* 218.1074.

(*E*)-7-Chloro-2-methyloct-2-en-1-ol. To a solution of above ester (1.09 g, 5 mmol) in dry toluene (1 mL) at 0 °C was added DIBAL-H (11 mL, 1 M in hexane, 11 mmol) dropwise via syringe. After 1 h at 0 °C, MeOH (10 mL) was added and the reaction was stirred 1 h at 23 °C. The mixture was diluted with ether, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, 33% EtOAc/hexane) to give 790 mg of alcohol as a clear oil: IR 3600, 3500 cm^{-1}; ^{1}H NMR δ 5.41 (1 H, br, t), 4.02 (2 H, s), 3.55 (2 H, t), 2.1–1.4 (8 H, m), 1.68 (3 H, br); MS calcd for $C_9H_{17}ClO$, *m/e* 176.0968; found, *m/e* 176.0968.

(*E*)-*O*-Acetyl-7-nitro-2-methyloct-2-en-1-ol. The alcohol was acetylated under standard conditions (Ac_2O, pyr) and converted to the nitro compound via the iodide by procedures as described above. This was purified by flash chromatography (SiO_2, 14% EtOAc/hexane): IR 1715, 1550, 1390 cm^{-1}; ^{1}H NMR δ 5.44 (1 H, br, t), 4.47 (2 H, s), 4.40 (2 H, t), 2.09 (3 H, s), 2.1–1.4 (8 H, m), 1.66 (3 H, br), the NMR revealed ~20% of the *Z* isomer was also present; MS calcd for $C_9H_{16}NO_2$ (M − OAc), *m/e* 170.1181; found, *m/e* 170.1181.

(52) House, H. O.; Crumrine, D. S.; Teranashi, A. Y.; Olmstead, H. D. *J. Am. Chem. Soc.* **1973**, *95*, 3310.

(53) Kinstle, T. H.; Mandanas, B. Y. *J. Chem. Soc., Chem. Commun.* **1968**, 1699. Wadsworth, D. H.; Schupp, O. E.; Seus, E. J.; Ford, J. A. *J. Org. Chem.* **1965**, *30*, 680.

Isoxazoline 35 was prepared by method A with nitro olefin (229 mg, 1 mmol), PhNCO (240 μL, 2.2 mmol), and Et_3N (35 μL) (72 h, 23 °C). The residue was purified by semipreparative HPLC (25% EtOAc/hexane) to give 170 mg (81%) of **35** as a clear oil: bp 70 °C (Kugel-Rohr, 0.4 mm). This was a 4/1 mixture of diastereomers resulting from the *E* and *Z* olefins: IR 1730 cm^{-1}; ^{1}H NMR (of major) δ 4.07 (2 H, AB quartet), 2.80 (2 H, m), 2.2–1.2 (7 H, m), 2.12 (3 H, s), 1.29 (3 H, s); MS, *m/e* 212 (M + 1), 138 (M − CH_2OAc), calcd for $C_8H_{12}NO$, *m/e* 138.0919; found, *m/e* 138.0919. Anal ($C_{11}H_{17}NO_3$) C, H.

Hydroxy Ketone 36. Reduction was performed by method 2 with isoxazoline **35** on usual 0.25-mmol scale to give 45 mg (82%) of **36** as a clear oil: bp 100 °C (Kugel-Rohr, 0.5 mm). The diastereomeric ratio (4/1) was identical with that of the starting material: IR 3500, 1730, 1690 cm^{-1}; ^{1}H NMR (of major) δ 4.20 (1 H, s), 4.04 (2 H, s), 2.7–1.4 (9 H, m), 2.11 (3 H, s), 1.22 (3 H, s); MS 215 (M + 1), 197 (M − OH), calcd for $C_{11}H_{17}O_3$, *m/e* 197.1178; found, *m/e* 197.1178. Anal ($C_{11}H_{18}O_4$) C, H.

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Registry No. 3a, 72553-35-6; **3b**, 7064-06-4; **3c**, 1017-09-0; **3d**, 86542-03-2; **3e**, 82419-99-3; **3f**, 86542-04-3; **4a**, 82150-00-3; **4b**, 5381-93-1; **4c**, 83670-89-7; **4d**, 86542-05-4; **4e**, 82150-01-4; **4f**, 86542-06-5; **7**, 86542-07-6; **8c**, 82150-07-0; **8t**, 82150-02-5; **9e**, 53496-45-0; **9t**, 53538-95-7; **10t**, 82150-03-6; **11t**, 82150-03-2; **12c**, 17669-23-7; **12t**, 17669-24-8; **13e**, 86542-08-7; **13t**, 86542-09-8; **14c**, 82150-08-1; **15e**, 82150-13-8; **16c**, 69423-36-5; **17e**, 32435-36-2; **18a**, 1569-94-4; **18b**, 86542-10-1; **18c**, 86542-11-2; **19a**, 86542-12-3; **19b**, 86542-13-4; **19c**, 86542-14-5; **23a**, 86542-15-6; **23b**, 86542-16-7; **24a**, 86542-17-8; **24b**, 86542-18-9; **27**, 73795-12-7; **28** (isomer 1), 86542-19-0; **28** (isomer 2), 86542-20-3; **29** (isomer 1), 86542-21-4; **29** (isomer 2), 86542-22-5; **30**, 86549-46-4; **31a**, 82150-04-7; **31b**, 82150-05-8; **31c**, 82150-06-9; **32a**, 26343-65-7; **32b**, 42052-56-2; **32c**, 26343-67-9; **33a**, 82150-10-5; **33b**, 82150-11-6; **33c**, 82150-12-7; **34a**, 26343-66-8; **34b**, 13161-18-7; **34c**, 26343-68-0; **35** (isomer 1), 86542-23-6; **35** (isomer 2), 82150-14-9; **36** (isomer 1), 86542-24-7; **36** (isomer 2), 82150-15-0; 1-hexene, 592-41-6; nitroethane, 79-24-3; nickel, 7440-02-0; phenylhydroximic acid chloride, 698-16-8; methylenecyclopentane, 1528-30-9; 1-nitropropane, 108-03-2; 2-methyl-1-pentene, 763-29-1; norcamphor, 497-38-1; 2-methylenebicyclo[2.2.1]heptane, 497-35-8; *endo*-2-allylbicyclo[2.2.1]heptan-2-ol, 61967-25-7; *trans*-2-butene, 624-64-6; *cis*-2-butene, 590-18-1; *trans*-4-octene, 14850-23-8; dihydropyran, 110-87-2; *tert*-butyldimethylchlorosilane, 18162-48-6; benzaldoxime, 932-90-1; 6-chloro-1-hexanol, 2009-83-8; 6-chlorohexanal, 52387-36-7; ethyltriphenylphosphonium bromide, 1530-32-1; (*E*)-1-chloro-6-octene, 86542-25-8; (*Z*)-1-chloro-6-octene, 86542-26-9; (*E*)-1-iodo-6-octene, 86542-27-0; (*Z*)-1-iodo-6-octene, 86542-28-1; (*E*)-1-nitro-6-octene, 86542-29-2; (*Z*)-1-nitro-6-octene, 86542-30-5; 5-chloropentanal, 20074-80-0; (*E*)-1-nitro-5-heptene, 86542-31-6; (*Z*)-1-nitro-5-heptene, 86542-32-7; benzyltriphenylphosphonium bromide, 1449-46-3; (*E*)-1-chloro-7-phenyl-6-heptene, 86542-33-8; (*Z*)-1-chloro-7-phenyl-6-heptene, 86542-34-9; (*E*)-1-nitro-7-phenyl-6-heptene, 86542-35-0; (*Z*)-1-nitro-7-phenyl-6-heptene, 86542-36-1; triethyl 2-phosphonopropionate, 3699-66-9; (*E*)-ethyl 7-chloro-2-methyl-2-octenoate, 86542-37-2; (*E*)-7-chloro-2-methyloct-2-en-1-ol, 86542-38-3; (*E*)-*O*-acetyl-7-nitro-2-methyloct-2-en-1-ol, 86542-39-4; (*Z*)-*O*-acetyl-7-nitro-2-methyloct-2-en-1-ol, 86542-40-7.