Norephedrine-Derived 2-Alkenyloxazolidines: Stereochemistry of Cyclization and Allylic Stereocenter Directed Asymmetric Conjugate Addition

Anna Bernardi,† Silvia Cardani,† Tullio Pilati,‡,§ Giovanni Poli,† Carlo Scolastico,*† and Roberto Villa†

Dipartimento di Chimica Organica e Industriale dell'Università, Centro CNR per lo Studio delle Sostanze Organiche Naturali, Via Venezian 21, 20133 Milano, Italy, and Centro per lo Studio delle Relazioni tra Struttura e Reattività Chimica, Via Golgi 19, 20124 Milano, Italy

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A study on the stereochemistry of the acid-catalyzed cyclization between N-protected norephedrine and α,β-unsaturated dimethyl acetals to give the title compounds is reported. Such heterocycles, on the basis of their different formation and reactivity behavior, are best classified as type I and type II oxazolidines, bearing electron-rich or -poor olefinic appendages respectively. The kind of catalyst as well as the reaction time dramatically affects the sense and the degree of the asymmetric cyclizations. Thermodynamic control is observed in the case of the type I cyclization products by using pyridinium tosylate (Py·Ts) as catalyst. In the type II series, on the contrary, Py·Ts-catalyzed cyclizations are shown to be kinetically controlled, whereas thermodynamic control is obtained when $BF_3{\cdot}Et_2O$ is used as catalyst. The mechanism and the factors determining the kinetic preference for the cis C_2/C_5 isomer are discussed. The addition of cuprate reagents to type II oxazolidine **3Ac** takes place with excellent π-face discrimination, affording, after nondestructive removal of the chiral auxiliary, 3-alkylsuccinaldehydic acid methyl esters in high enantiomeric purity. Experimental evidence, together with theoretical considerations, provides a reasonable rationalization for the observed selectivity of the conjugate addition.

Introduction

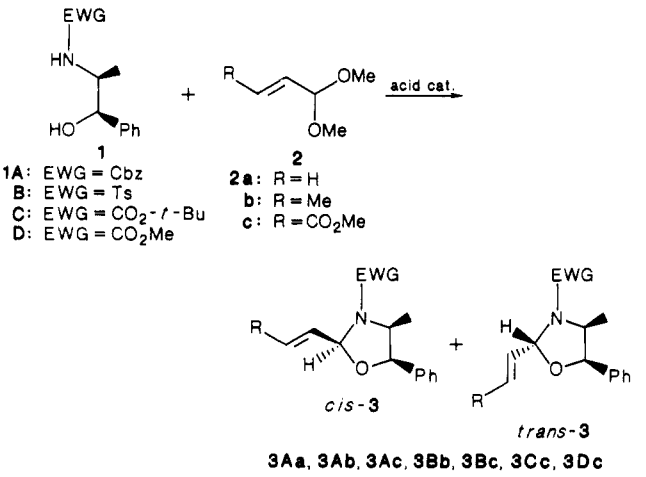
The chiral masking of an α,β-unsaturated aldehyde may be easily achieved through the incorporation of the carbonylic carbon into the C_2 of a suitable chiral oxazolidinic ring.[1,2] The newly generated allylic center, when stereohomogeneously obtained, can in turn direct useful asymmetric transformations at the vicinal olefinic carbon. The chiral auxiliary may easily be split off in a second stage, thus releasing the free carbonylic function.

The availability of both the chiral auxiliary antipodes, their recycling, and high values of asymmetric induction and chemical yields are the obvious features that give synthetic value to the above approach.

We recently reported the exploitation of this type of strategy in the asymmetric cis-dihydroxylation of norephedrine-derived 2-alkenyloxazolidines of type I and type II. Owing to the different behavior in both formation and reactivity, we arbitrarily classify, for convenience, these heterocycles as type I and type II oxazolidines according to the absence or the presence respectively of an electron-withdrawing group on the distal ($C_{2'}$) olefinic carbon (Figure 1). Type I and type II oxazolidines are both obtained from (benzyloxycarbonyl)norephedrine (Cbz-norephedrine) and the corresponding dimethyl acetals of some α,β-unsaturated aldehydes.[3,4]

These newly designed heterocycles feature perfect water and silica gel stability and a high degree of asymmetric induction in their formation (vide infra); furthermore, they can easily be obtained as pure diastereomers. Such behavior is quite remarkable in view of the fact that the corresponding type I ephedrine-derived oxazolidines (*N*-methyloxazolidines), although formed in high diastereomeric purities, undergo water and silica gel promoted cleavage. An attempt toward the stereoselective synthesis of the type II ephedrine-derived oxazolidine A (Figure 2)

Scheme I. Synthesis of Type I and Type II 3



3Aa, 3Ab, 3Ac, 3Bb, 3Bc, 3Cc, 3Dc

resulted in a 5:1 equilibrium ratio of unseparable epimeric material.

Results and Discussion

Stereochemistry of the Cyclization. The cyclization between the N-protected norephedrines **1A–D** and the

† Centro CNR per lo Studio delle Sostanze Organiche Naturali.
‡ Centro per lo Studio delle Relazioni tra Struttura e Reattività.
§ Author to whom correspondence about X-ray crystal structure should be addressed.

(1) (a) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron* **1984**, *40*, 1803 and references therein. (b) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537 and references therein. *J. Chem. Soc., Chem. Commun.* **1983**, 1485.
(2) Baudet, M.; Gelbcke, M. *Anal. Lett.* **1979**, *12*(B4), 325 and **1979**, *12*(B6), 641.
(3) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* **1985**, *26*, 5459.
(4) Chiral ephedrine-derived oxazolidines, bearing an unsaturated double bond, have been used in asymmetric syntheses: (a) Huche, M.; Aubouet, J.; Pourcelot, G.; Berlan, J. *Tetrahedron Lett.* **1983**, *24*, 585. (b) Berlan, J.; Besace, Y.; Stephan, E.; Cresson, P. *Tetrahedron Lett.* **1985**, *26*, 5765. (c) Berlan, J.; Besace, Y.; Pourcelot, G.; Cresson, P. *Tetrahedron* **1986**, *42*, 4757. (d) Berlan, J.; Besace, Y. *Tetrahedron* **1986**, *42*, 4767. (e) Mangeney, P.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1983**, *24*, 373. (f) Abdallah, H.; Gee, R.; Carrie, R. *Tetrahedron Lett.* **1982**, *23*, 503.

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Table I. Stereoselectivity of Cyclization to 3

entry	EWG	R	rctn condtns[a]	cis:trans	product	yield, %
1	Cbz	Me	15 min; A[b]	92:8[c]	**3Ab**	
2	Cbz	Me	4 h; A[b]	76:24[c]	**3Ab**	80
3	Cbz	Me	24 h;B	97.5:2.5[c]	**3Ab**	27
4	Cbz	CO_2Me	12 h; A	94:6[d]	**3Ac**	88
5	Cbz	CO_2Me	15 min; C	94:6[d]	**3Ac**	95
6	Cbz	CO_2Me	2 h; C	81:19[d]	**3Ac**	
7	Cbz	CO_2Me	18 h; C	73:27[d]	**3Ac**	
8	Boc	CO_2Me	20 h; A	93:7[d]	**3Cc**	65
9	Boc	CO_2Me	30 min; D	97:3[d]	**3Cc**	98
10	Ts	Me	4 h; A	≥95:5[e]	**3Bb**	88
11	Cbz	H	5 h; A	≥95:5[e]	**3Aa**	91
12	Ts	CO_2Me	18 h; A	≥95:5[e]	**3Bc**	85
13	CO_2Me	CO_2Me	15 min; C	≥95:5	**3Dc**	87

[a] Reaction conditions: A, 0.3 molar equiv of pyridinium tosylate (Py·Ts), reflux; B, 0.3 molar equiv of Py·Ts, CH_2Cl_2, 30 °C; C, 3.0 molar equiv of $BF_3{\cdot}Et_2O$, PhH, room temperature; D, 3 molar equiv of $BF_3{\cdot}Et_2O$, PhH, 0 °C. [b] Partial conversion. [c] Determined by HPLC analysis. [d] Determined by capillary GC analysis. [e] Determined by ^1H and ^{13}C NMR spectroscopy.

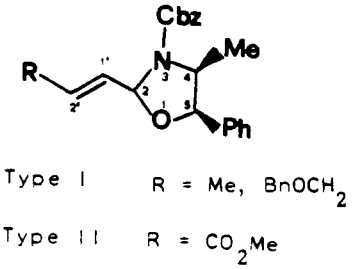


Figure 1.

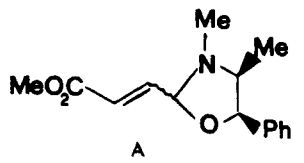


Figure 2.

dimethyl acetals **2a–c**, in the presence of pyridinium tosylate as acidic catalyst, required several hours of refluxing in benzene. The expected 2-alkenyloxazolidines **3** with a constant preference for the cis isomer were obtained (Scheme I; Table I).

The absolute configuration at C_2 of **3Ab** and **3Ac** has been determined via NOE difference measurements. Thus upon irradiation of the major isomers at Me-C_4, both olefinic protons gave rise to a positive NOE difference. Alternatively, irradiation of Me-C_4 in the minor isomer of **3Ab** caused a positive NOE difference for H-C_2.

The absolute configuration of oxazolidine **3Bc** was determined by its X-ray diffraction (Figure 3).

When the formation of **3Ab** with varying times, in refluxing PhH, was studied, the initial 92:8 cis:trans ratio, observed after 15 min, changed to 87:13 after 30 min and reached a 76:24 stable ratio after 4 h (Table I, entries 1 and 2). Since the same ratio was found by separately submitting the two isomers of **3Ab** to the same conditions, it is apparent that MeOH released during the cyclization is not involved in the isomerization process. When the same cyclization was performed at room temperature in CH_2Cl_2, a 97.5:2.5 cis:trans ratio was produced, albeit at the expense of the conversion (Table I, entry 3).

Oxazolidine **3Ac** has been obtained with a 94:6 cis:trans ratio by using either Py·Ts or $BF_3{\cdot}Et_2O$ as the acidic catalyst (Table I, entries 4 and 5); while such a ratio was found to be independent of the reaction time when the former conditions were applied, prolonged standing in the presence of $BF_3{\cdot}Et_2O$ shifted the initial ratio to a 73:27 cis:trans equilibrium ratio (Table I, entries 5–7).

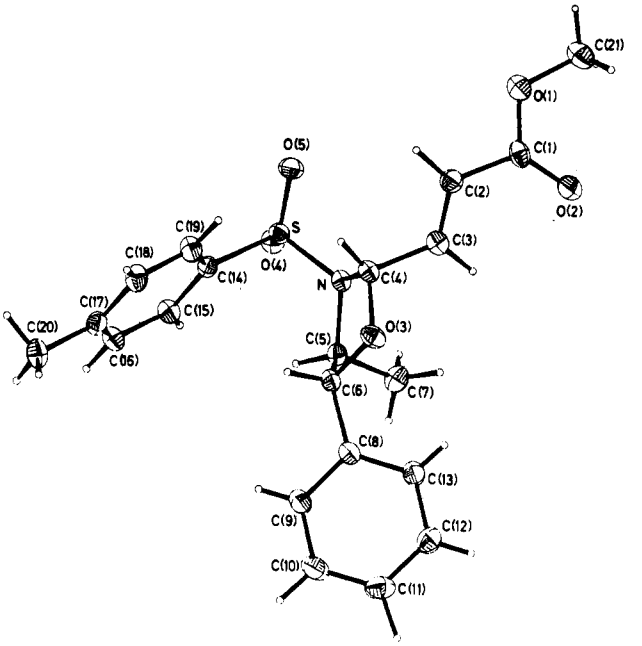
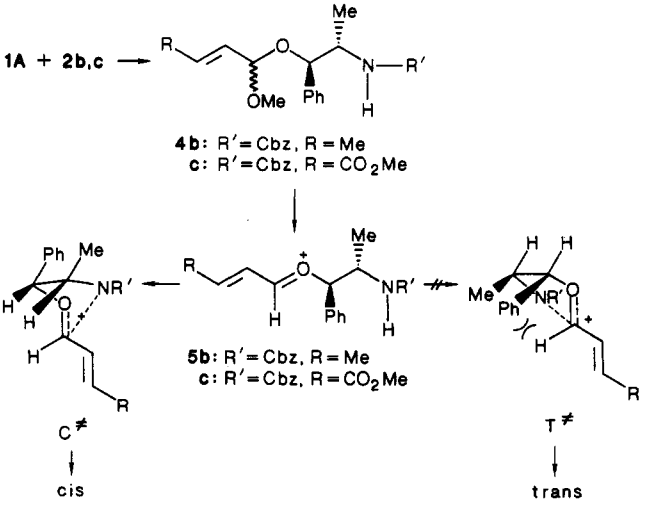


Figure 3.

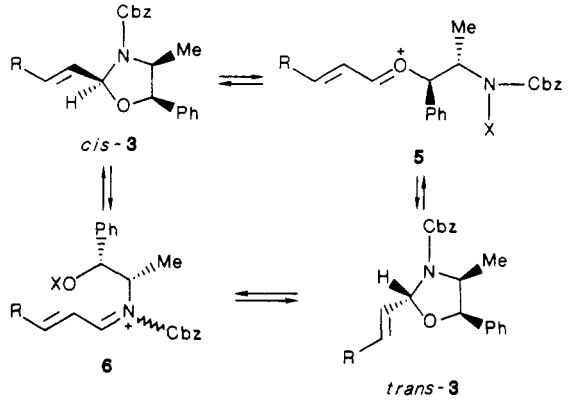
Scheme II. Proposed Kinetic Pathway to 3



In contrast to the mechanism of the cyclization between ephedrine and aldehydes,[1b,5] where an iminium ion has

(5) For a review on *N*-acyliminium intermediates, see: Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

Scheme III. Acid-Catalyzed Equilibration of 2-Alkenyloxazolidines 3[a]



[a] X = H, BF_3^-; R = Me, CO_2Me.

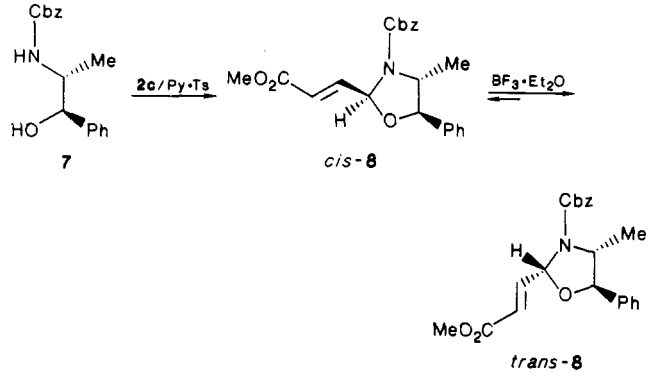
been shown to be involved, the formation of a diastereomeric mixture of the isolable mixed acetals **4**[6] is the first step of the cyclization under study. Such intermediates, showing an absorption in the IR region at 3430 cm^{-1} and no exchangeable signal by D_2O treatment in ^1H NMR spectroscopy, readily cyclize to the corresponding oxazolidines **3** when heated in PhH in the presence of Py·Ts. The subsequent ring closure should therefore proceed through an oxonium ion of type **5**,[7] which in turn can cyclize via a 5-*Endo-Trig* process[8] (Scheme II).

We believe that the kinetic preference for the *cis*-oxazolidine is due to steric hindrance factors during the formation and the cyclization of the transient oxonium ion **5**.[9] In fact, while the transition structure C‡, leading to the cis isomer, is relatively devoid of steric congestion, in the alternative T‡ structure, leading to the trans isomer, the aromatic ring experiences an unfavorable interaction with the aldehydic proton. Such destabilization cannot be overcome by the phenyl ring rotation owing to the blocking vicinal methyl group[10] (Scheme II).

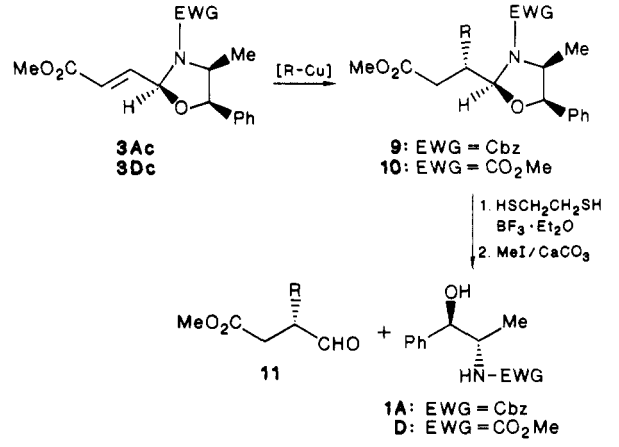
Inspection of Table I reveals that kinetic control in the cyclization is obtained only for type II products and when Py·Ts is used as the catalyst (Table I, entry 4). On the other hand, prolonged reaction times in the Py·Ts and BF_3·Et_2O mediated cyclizations, giving respectively type I and type II products, afford thermodynamic ratios (Table I, entries 1, 2, and 5–7).

While the factors determining the kinetic preference for the cis isomer have already been presented, equilibration through an oxonium ion **5** or an acyliminium ion **6**[5] can account for the observed thermodynamic control[11] (Scheme III). It is worth noting that the cis isomer is favored by kinetic as well as thermodynamic conditions.

Scheme IV. Cyclization of (1*R*,2*R*)-Cbz-norpseudoephedrine 7



Scheme V. Cuprate Addition to 3Ac and 3Dc and Chiral Auxiliary Removal[a]



[a] **a**, R = Me; **b**, R = Bu; **c**, R = Et; **d**, R = *n*-Pr; **e**, R = vinyl; **f**, R = allyl.

According to the hypothesis shown in Scheme II, the kinetic preference of the cyclization should be governed only by the stereocenter linked to the oxygen atom. It follows that the kinetic formation of the oxazolidines deriving from a suitably N-protected norpseudoephedrine should favor the formation of the C_2/C_5 cis isomer. Indeed, reaction between (1*R*,2*R*)-Cbz-norpseudoephedrine **7** and the acetal **2c** in the presence of Py·Ts gave oxazolidine **8** in a 98.7:1.3 C_2/C_5(cis):C_2/C_5(trans) ratio. Again, exposure of this material to 3.0 molar equiv of BF_3·Et_2O at room temperature in PhH for 1.5 h afforded the expected isomer interconversion until a 10:90 cis:trans thermodynamic ratio was reached (Scheme IV).

Thus, in contrast with the previous examples, kinetic and thermodynamic conditions give opposite diastereomeric preferences.

The absolute configuration assignment of oxazolidines **8** relies upon ^1H NMR spectroscopy. In fact, owing to the rotational constraint of the C_5–Ph bond, H-C_2 in cis **8** appears 0.7 ppm shielded with respect to the corresponding proton in the trans isomer.[2] Furthermore, irradiation of H-C_5 gave rise to a positive NOE difference for H-C_2 in the **8** cis isomer and for H-$C_{1'}$ in the **8** trans isomer.

(6) An analytical sample of **4c** could be obtained in pure form by flash chromatography of the crude reaction mixture, provided that cyclization is quenched after 4 h. **4b** could be isolated by performing the corresponding cyclization at room temperature and by subsequent preparative TLC purification. The latter mixed acetal shows a great tendency to cyclize by simple heating or in the presence of acids in traces.

(7) The participation of an *N*-acyliminium ion species at this stage (vide infra), although it cannot be ruled out, seems rather unlikely.

(8) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.

(9) Actually, **5** could in principle be present as the *E* as well as the *Z* geometric isomer. However, in line with the geometry observed in aldehyde–Lewis acid complexes, the former isomer should be largely favored. For aldehyde–Lewis acid complexes, see: Reetz, M. T.; Hullmann, M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. Raber, D. J.; Raber, N. K.; Chandrasekhar, J.; Schleyer, P. v. R. *Inorg. Chem.* **1984**, *23*, 4076. Childs, R. F.; Mulholland, D. L.; Nixon, A. *Can. J. Chem.* **1982**, *60*, 801.

(10) (a) The Ph–C5 rotational barrier in **3Ac** was estimated to be 70 kcal/mol by semiempirical methods (PCILO): Tosi, C., personal communication. (b) Meister, C.; Shen, Z.; Scharf, H. D. *Liebigs Ann. Chem.* **1984**, 147.

(11) The thermodynamic stability of the cis isomer in similar five-membered rings is well documented: Reference 1b. Mashraqui, S. H.; Kellogg, R. M. *J. Org. Chem.* **1984**, *49*, 2513. Naef, R.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 135 and **1981**, *64*, 2704. Becket, A. H.; Jones, G. R. *Tetrahedron* **1977**, *33*, 3133.

Table II. Me_2CuLi Addition to 3Dc

entry	equiv of Bu_3P	diast ratio[a]	config[b]	yield, %
1	0	97.6:2.4	S	70
2	1	97.5:2.5	S	88
3	4	97.5:2.5	S	68

[a] Determined by capillary GC analysis. [b] Determined by conversion of 10 into (S)-11a as reported for 9a (see text).

Regardless of the pathway involved in Scheme III, it is apparent that type I oxazolidines can readily equilibrate upon prolonged exposure to Py·Ts, whereas the electron-withdrawing group (EWG) of type II oxazolidines **3Ac** or 8 disfavors the formation of the presumed allylic ion to the point that Py·Ts equilibration is no more allowed (Table I, entry 4). Nevertheless, equilibration may be established in the presence of the stronger Lewis acid BF_3·Et_2O (Table I, entries 5–7; Scheme IV).

Addition of Cuprate Reagents. The addition of nucleophile reagents to conjugated olefins bearing an allylic stereocenter is a problem that has been receiving considerable attention from both theoretical and experimental points of view.[12,13]

The study of conjugate additions to type II oxazolidines, expected for electronic reasons to take place at $C_{1'}$, thus appeared to be of particular interest.[14]

We reported in a recent paper[15] that cuprate reagents cleanly add to oxazolidine *cis*-**3Ac** with excellent regio- and stereoselectivity (diastereomeric ratio ≥95:5) to give, in good yields, esters **9a–f** (Scheme V).

Although the mechanism of organocopper conjugate addition is still an open question, convincing recent evidence shows the reversible formation of a cuprate–substrate (d–π*) complex and a Cu^{III} β-adduct in the initial step.[12d,16,17] However, the presence of TMSCl in the reaction medium can irreversibly trap the latter intermediate, thereby shifting the rate-determining step (rds) from the reductive elimination level to the earlier d,π* complexation stage.[12d,18]

Cuprate additions to oxazolidine **3Ac** always occurred from the substrate *si* face; moreover, the same selectivity was observed regardless of the presence (3 molar equiv) or absence of TMSCl. It follows that the postulated kinetic β-adduct must be the more stable (d–π* complexation as rds) or the faster reacting diastereomer (reductive elimination as rds).

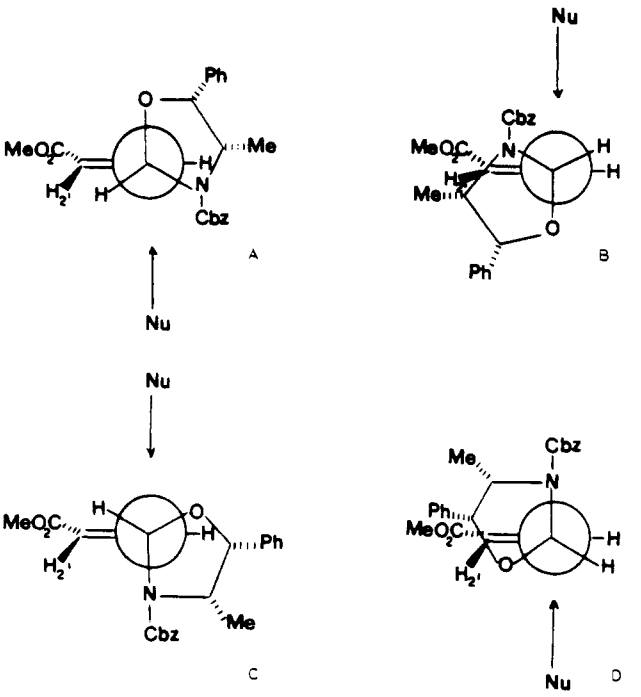


Figure 4. Proposed transition structures for the cuprate addition.

Me_2CuLi addition to oxazolidine **3Dc** in the presence of varying amounts of PBu_3, to give **10**, showed that selectivity is unaffected by the presence of such a strong coordinating agent for cuprates[4d] (Scheme V, Table II). Furthermore, the $(CH_2CH)_2CuLi$ addition to oxazolidine **3Ac** occurred with the constant virtually quantitative *si*-face discrimination, despite the fact that it was carried out in the presence of a Cu coordinator such as Me_2S (Me_2S/Et_2O as solvent). These results allowed us to rule out a possible coordination-directed mechanism.

Accordingly, the stereochemical outcome of these additions can be interpreted in terms of stereoelectronically and/or sterically controlled kinetic π-face differentiation. The four staggered transition structures A–D were thus considered (Figure 4). On the basis of MO considerations, the LUMO of the electrophile is favorably affected through the mixing of the π* orbital with the lowest energy σ* orbital which is associated with the most electronegative substituent, e.g., oxygen.[19] For such an effect to operate, the electronegative substituent must occupy the perpendicular positions, as happens in A and B.[19] On the other hand, it is evident that $H_{2'}$–ring interactions destabilize B and D. Structure A, leading to the observed stereochemistry, therefore appears to be the only transition state fulfilling both stereoelectronic and steric requirements. p nucleophiles would very likely disfavor structure A because of their unfavorable interaction along the Bürgi–Dunitz trajectory.[19] Cuprates, on the contrary, owing to the binodal symmetry and high diffuseness of their d orbitals,[15,16] are not expected to follow such a trajectory.[20] Therefore, the above-cited trajectory–destabilization of structure A should not be taken into account in this case.

(12) Allylic stereocenter directed asymmetric inductions: (a) Trost, B. M.; Lynch, J.; Renaut, P. *Tetrahedron Lett.* **1985**, *26*, 6313 and references therein. (b) Roush, R. H.; Lesur, M. B. *Tetrahedron Lett.* **1983**, *24*, 2231 and references therein. (c) Heathcock, C. H.; Kiyooka, S.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, *49*, 4214. Heathcock, C. H.; Uehling, D. E. *J. Org. Chem.* **1986**, *51*, 279. (d) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015. (e) Leonard, J.; Ryan, G. *Tetrahedron Lett.* **1987**, *28*, 2525.

(13) Leading references on asymmetric 1,4 organometallic reagents additions: Tomioka, K.; Koga, K. *Asymmetric Synthesis*: Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 201. Posner, G. H. *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1983; Vol. 2, p 225. Lutomsky, K. A.; Meyers, A. I. *Asymmetric Synthesis*: Academic: New York, 1984; Vol. 3, p 213. Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. *Helv. Chim. Acta* **1985**, *68*, 212. Soai, K.; Machida, H.; Ookawa, A. *J. Chem. Soc., Chem. Commun.* **1985**, 469. Tomioka, K.; Sudani, M.; Shinmi, Y.; Koga, K. *Chem. Lett.* **1985**, 329. Enders, D.; Papadopoulos, K. *Tetrahedron Lett.* **1983**, *24*, 4967. Leyendecker, F.; Laucher, D. *Tetrahedron Lett.* **1983**, *24*, 3517. Cram, D. J.; Sogah, G. D. Y. *J. Chem. Soc., Chem. Commun.* **1981**, 625. Tomioka, K.; Suenaga, T.; Koga, K. *Tetrahedron Lett.* **1986**, *27*, 369. Heathcock, C. H.; Henderson, M. A.; Oare, D. A.; Sanner, M. A. *J. Org. Chem.* **1985**, *50*, 3019. Heathcock, C. H.; Oare, D. A. *J. Org. Chem.* **1985**, *50*, 3022. Heathcock, C. H.; Norman, M. H.; Uehling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797. Oppolzer, W.; Poli, G.; Bernardinelli, G.; Kingma, A. J.; Starkemann, C. *Helv. Chim. Acta* in preparation.

(14) Cuprate reagents add to emphedrine-derived 2-alkenyloxazolidines at the distal $C_{2'}$ olefinic position with fairly good selectivities: see ref 5a–e.

(15) Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5041.

(16) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063.

(17) (a) Hallnemo, G.; Olsson, T.; Ullenius, C. *J. Organomet. Chem.* **1985**, *282*, 133. (b) Hallnemo, G.; Ullenius, C. *Tetrahedron Lett.* **1986**, *27*, 395. (c) Krauss, S. R.; Smith, S. G. *J. Am. Chem. Soc.* **1981**, *103*, 141.

(18) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6019.

(19) Anh, N. T. *Top. Curr. Chem.* **1980**, *88*, 145 and references therein.

(20) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Siebermann, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.

Addition of the copper reagent deriving from vinylmagnesium bromide and CuI proceeded with the same π-face discrimination and comparable yield as the reaction of (divinylcopper)lithium, the only proviso being that the addition is performed at a lower temperature.

It is also worth noting that, in contrast to the several examples shown in the literature,[21] (diallylcopper)lithium exhibited the same sense of diastereoface selection as the other aliphatic and vinyl reagents.

For correlation purposes (vide infra), adducts **9e** and **9f** were transformed into **9c** and **9d** respectively by 5% Rh/alumina catalyzed hydrogenation.

A straightforward nondestructive removal of the chiral auxiliary completed the whole task. Accordingly, treatment of adducts **9a–d** with $HSCH_2CH_2SH/BF_3{\cdot}Et_2O$ in CH_2Cl_2 smoothly released the intact auxiliary **1A** together with the corresponding dithiolanes.[22] Immediate submission of the crude reaction mixtures to standard thioacetal hydrolysis ($CaCO_3/MeI/H_2O$) gave the known (*S*)-3-alkylsuccinaldehydates **11a–d**,[23] thereby unveiling the constant *si*-face selectivity of the cuprate additions as well as the effectiveness of the deprotection steps (Scheme V). For configuration assignment, **11a** was reduced to the known (2*S*)-2-methylbutane-1,4-diol.[24]

Conclusions

Suitably N-protected norephedrines cyclize stereoselectively under acidic catalysis with α,β-unsaturated dimethyl acetals, affording 2-alkenyloxazolidines.

Such heterocycles, on the basis of their different formation and reactivity behavior and according to the presence or absence of an EWG on the distal olefinic carbon, fall into two different classes.

The cyclization conditions dramatically affect the sense and the degree of the asymmetric induction. 2-Alkenyloxazolidines, which can be regarded as new chiral masked α,β-unsaturated aldehydes, feature perfect water and silica gel stability and can easily be obtained as pure diastereomers.

The addition of several cuprate reagents to oxazolidine **3Ac** occurs with excellent and predictable π-face selectivity, which has been rationalized on the basis of experimental evidence as well as MO considerations. The adducts obtained from the conjugate additions can, in turn, be transformed into 3-alkylsuccinaldehydates in high % ee by a two-step procedure that allows the recovering of the intact chiral auxiliary.

Experimental Section

^1H NMR spectra were recorded with a Varian XL-200 or a Bruker WP-80 instrument, and ^{13}C NMR spectra were recorded with a Varian XL-200 instrument in the FT mode with tetramethylsilane as internal standard. Optical rotations were measured in 1-dm cells of 1-mL capacity by using a Perkin-Elmer 241 polarimeter. Elemental analyses were performed with a Perkin-Elmer 240 instrument. Silica gel 60 F_{254} plates (Merck) were used for analytical TLC and 270–400-mesh silica gel (Merck) was used for flash chromatography. GLC analyses were performed on a Dani 6500 instrument with a capillary OV-1 column (15 m) using a Hewlett-Packard 3390A integrator. HPLC analyses were performed on a Varian 500 instrument with a LiChrosorb column and a UV (254-nm) detector using a Hewlett-Packard 3390A integrator. Organic extracts were dried over Na_2SO_4 and filtered before removal of the solvent under reduced pressure. "Dry" solvents were distilled under dry N_2 just before use: tetrahydrofuran (THF) and Et_2O were distilled from sodium metal in the presence of benzophenone ketyl, and benzene was distilled from sodium metal and CH_2Cl_2 from CaH_2. All reactions employing "dry" solvents were run under a nitrogen (from liquid N_2) atmosphere. Dimethyl acetals **2a–c** were prepared according to ref 25. The aldehyde related to dimethyl acetal **2c** was obtained according to ref 26.

N-Protected Norephedrines. 1A–D and **7** were obtained by using respectively L-norephedrine or (1*R*,2*S*)-norpseudoephedrine under standard Schotten–Baumann conditions.

1A. The crude product was used without further purification in the subsequent reactions: yield 99%; mp 111–113 °C; $[\alpha]^{25}_D$ −38.7° (*c* 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.05 (3 H, d, J = 6.9 Hz), 1.53 (1 H, br s), 2.50–3.10 (1 H, m), 3.90–4.40 (1 H, m), 4.90 (1 H, d, J = 3.2 Hz), 5.13 (2 H, s), 7.35 (10 H, s); IR ($CHCl_3$) ν 3610, 3460, 1710, 1500, 1450 cm^{-1}.

1B. The reaction was carried out by using Et_2O as cosolvent. The crude product was purified by flash chromatography (CH_2Cl_2/acetone, 92:8) and then crystallized from *n*-hexane/Et_2O, affording the pure product in 70% yield: mp 86–88 °C; $[\alpha]^{25}_D$ −14.5° (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.84 (3 H, d, J = 6.9 Hz), 1.50 (1 H, br s), 2.40 (3 H, s), 3.30–3.80 (1 H, m), 4.75 (1 H, d, J = 4.0 Hz), 4.80 (1 H, br s), 7.30 (5 H, s), 7.30–7.85 (4 H, m); IR ($CHCl_3$) ν 3600, 3500, 3370, 1595, 1490 cm^{-1}.

1C. The crude product was crystallized from Et_2O/hexane (75% yield): mp 88–89 °C; $[\alpha]^{25}_D$ −63.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$/50 °C) δ 0.97 (3 H, d, J = 6.9 Hz), 1.44 (9 H, s), 3.12 (1 H, br s), 3.80–4.18 (1 H, m), 4.61 (1 H, br s), 4.85 (1 H, d, J = 2.6 Hz), 7.31 (5 H, s); IR ($CHCl_3$) ν 3600, 3440, 1700, 1500, 1450, 1360, 1150 cm^{-1}.

1D. The crude product was used without further purification for the subsequent reactions: yield 98%; mp 88–90 °C; $[\alpha]^{25}_D$ −52.7° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 6.6 Hz), 1.55 (1 H, br s), 2.60 (1 H, br s), 3.66 (3 H, s), 3.80–4.25 (1 H, m), 4.85 (1 H, d, J = 3.0 Hz), 7.33 (5 H, s); IR ($CHCl_3$) ν 3600, 3440, 1710, 1520, 1450 cm^{-1}.

7. The crude product was crystallized twice from Et_2O/hexane, affording the product in 80% yield: mp 83–85 °C; $[\alpha]^{25}_D$ −34.3° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3/D_2O$) δ 1.12 (3 H, d, J = 7.0 Hz), 4.00 (1 H, m), 4.60 (1 H, d, J = 4.0 Hz), 4.90 (1 H, br d), 5.05 (2 H, s), 7.30 (10 H, s); IR ($CHCl_3$) ν 3600, 3440, 1710, 1500, 1450 cm^{-1}.

Cyclizations. For cis:trans diastereomeric ratios and isolated yields, see Table I.

General Procedure A. To a solution of N-protected L-norephedrine or (1*R*,2*R*)-norpseudoephedrine (1 mmol) in dry benzene (10 mL) were added pyridinium tosylate (0.3 mmol) and dimethyl acetal (1.0–1.1 mmol). The mixture was refluxed for the proper time (see Table I) with a bypassed dropping funnel filled with 4-Å molecular sieves placed between the flask and the reflux condenser. The mixture was cooled and, after Et_2O (10 mL) addition, filtered and the filtrate washed with a 5% aqueous $NaHCO_3$ solution and brine and dried over Na_2SO_4. The mixture was filtered and the solvent evaporated under reduced pressure.

General Procedure C. To a solution of dimethyl acetal (1 mmol) and the N-protected amino alcohol (1 mmol) in 10 mL of dry benzene was added $BF_3{\cdot}Et_2O$ (3.0 mmol), and the mixture was stirred at room temperature for the proper time (see Table I). The reaction mixture was quenched with a 5% aqueous $NaHCO_3$ solution, extracted with AcOEt, dried over Na_2SO_4, and filtered and the solvent evaporated under reduced pressure.

Cyclization Product Characterizations. *cis*-3Aa. The crude product was purified by flash chromatography (hexane/AcOEt, 85:15): $[\alpha]^{25}_D$ −62.1° (*c* 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.83 (3 H, d, J = 6.6 Hz), 4.15–4.50 (1 H, m), 5.20 (2 H, s),

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5.10–6.20 (5 H, m), 7.33 (10 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 16.0, 55.9, 66.9, 81.2, 88.3, 119.1, 135.7, 135.9, 153.1; IR ($CHCl_3$) ν 3170, 3060, 1790, 1500, 1450, 1220 cm^{-1}. Anal. Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.32; H, 6.60; N, 4.31.

3Ab. The diastereomeric ratios were determined on the crude mixture by HPLC analysis (hexane/AcOEt, 90:10, flow 1.5 mL/min, t_R = 4.16 (trans isomer), 5.43 (cis isomer)). Flash chromatography purification (hexane/AcOEt, 90:10) afforded pure *trans*- (the first eluted) and *cis*-**3Ab**.

***cis*-3Ab**: ^{1}H NMR ($CDCl_3$/40 °C) δ 0.86 (1 H, d, J = 6.7 Hz), 1.75 (3 H, dd, J = 5.4 Hz, J = 1.0 Hz), 4.30 (1 H, dq, J = 5.8 Hz, J = 6.7 Hz), 5.08 (1 H, d, J = 5.8 Hz), 5.18 (2 H, d, J = 1.9 Hz), 5.40–6.20 (3 H, m), 7.30 (5 H, s), 7.33 (5 H, s); ^{13}C NMR ($CDCl_3$/40 °C) selected data δ 16.0, 17.5, 55.9, 66.9, 81.0, 88.7, 131.6, 136.1, 136.4, 153.1; $[\alpha]^{25}_D$ −60.8° (c 1.3, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.79; H, 6.80; N, 4.10.

***trans*-3Ab**: ^{1}H NMR ($CDCl_3$/40 °C) δ 0.85 (3 H, d, J = 6.5 Hz), 1.75 (3 H, dd, J = 5.4 Hz, J = 1.0 Hz), 4.21 (1 H, dq, J = 6.0 Hz, J = 6.5 Hz), 5.17 (2 H, d, J = 3.5 Hz), 5.30 (1 H, d, J = 6.0 Hz), 5.40–6.10 (3 H, m), 7.33 (10 H, s); ^{13}C NMR ($CDCl_3$/40 °C) selected data δ 14.4, 17.4, 55.6, 66.8, 79.6, 87.5, 129.7, 136.1, 136.4, 152.5. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.78; H, 6.90; N, 4.14.

3Ac. The crude product can be purified by flash chromatography (hexane/AcOEt, 80:20). The diastereomeric ratios were determined by capillary GC analysis (ISO 240 °C, t_R = 10.21 (cis isomer), 10.91 (trans isomer)).

***cis*-3Ac**: ^{1}H NMR ($CDCl_3$/50 °C) δ 0.83 (3 H, d, J = 6.5 Hz), 3.75 (3 H, s), 4.33 (1 H, dd, J = 6.5 Hz, J = 6.0 Hz), 5.15 (1 H, d, J = 5.3 Hz), 5.18 (2 H, s), 5.70 (1 H, d, J = 5.3 Hz), 6.25 (1 H, d, J = 16 Hz), 6.95 (1 H, dd, J = 16 Hz, J = 5.3 Hz), 7.33 (10 H, s); ^{13}C NMR ($CDCl_3$/50 °C) selected data δ 16.0, 51.5, 55.8, 67.2, 81.6, 86.0, 124.0, 135.4, 136.0, 143.2, 152.8, 165.9; IR ($CHCl_3$) ν 2990, 2970, 2940, 1700, 1410, 1405, 1350, 1020 cm^{-1}; $[\alpha]^{25}_D$ −81.6° (c 1, $CHCl_3$). Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.29; H, 6.10; N, 3.65.

***trans*-3Ac**: ^{1}H NMr ($CDCl_3$/50 °C) selected data δ 3.73 (3 H, s), 5.28 (1 H, d, J = 5.1 Hz), 5.86 (1 H, d, J = 4.8 Hz); ^{13}C NMR ($CDCl_3$/50 °C) selected data δ 55.6, 123.05, 136.1.

***cis*-3Bb.** The crude product was purified by flash chromatography (hexane/AcOEt, 85:15): mp 81–83 °C; $[\alpha]^{25}_D$ −54.4° (c 2.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.82 (3 H, d), 1.76 (3 H, dd), 2.43 (3 H, s), 3.95–4.30 (1 H, m), 4.44 (1 H, d), 5.40 (1 H, d), 5.55–6.25 (2 H, m), 7.25 (5 H, s), 7.30–7.85 (4 H, m). Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.23; H, 6.50; N, 3.90.

***cis*-3Bc.** The crude product was purified by flash chromatography (hexane/AcOEt, 85:15): ^{1}H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.0 Hz), 2.45 (3 H, s), 3.80 (3 H, s), 4.10 (1 H, dd, J = 6.0 Hz, J = 5.4 Hz), 4.43 (1 H, d, J = 5.4 Hz), 5.60 (1 H, dd, J = 5.4 Hz, J = 1.0 Hz), 6.30 (1 H, dd, J = 1.0 Hz, J = 16.0 Hz), 7.0 (1 H, dd, J = 16.0 Hz, J = 5.4 Hz), 7.05–7.45 (7 H, m), 7.75–7.90 (2 H, m); IR ($CHCl_3$) ν 1730, 1600, 1450, 1430, 1350 cm^{-1}; $[\alpha]^{25}_D$ −51.9° (c 0.9, $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.83; H, 5.77; N, 3.49. Found: C, 62.80; H, 5.79; N, 3.47. Crystal data: $C_{21}H_{23}NO_5S$, M_r 401.5, monoclinic, $P2_1$, a = 8.222 (1) Å, b = 11.069 (3) Å, c = 11.276 (1) Å, β = 96.46 (1)°, V 1019.7 (3) Å^3, Z = 2, D_x = 1.308 g cm^{-3}, μ = 1.8 cm^{-1}, $F(000)$ = 424, room temperature; 2462 unique reflections were collected up to θ = 27.5 on a Nonius CAD4 diffractometer with graphite-monochromated Mo Kα radiation, λ = 0.71069 Å, $\theta/2\theta$ technique. Three standard reflections do not show any decay; corrections for Lorentz and polarization effects were applied; 2225 data with $I > \sigma(I)$ were considered observed and used in crystal analysis. The structure was solved by direct methods, using the MULTAN80 program: 18 of the 28 heavy atoms were obtained from the best E map, while the reacting ions and H atoms were derived from Fourier difference maps. Heavy atoms were refined anisotropically, H atoms isotropically. The quantity minimized was $\sum w(F_o - F_c)^2$, with weight $w = 4F^2/[\sigma^2(F^2) + 0.0004F_o^4]$. Scattering factors for neutral atoms were taken from: *International Tables for X-ray Crystallography*; Kynoch: Birmingham, England, 1974; Vol. IV, pp 149–150. The maximum Δ/σ in the last least-squares cycle of refinement was <0.05, and the maximum residue on the final difference Fourier map was about 0.2 e/Å^3. Final discrepancy indexes were R = 0.034 and R_w = 0.036.

***cis*-3Cc.** The product was purified by flash chromatography (hexane/AcOEt, 85:15). The cis:trans diastereomeric ratio was obtained by capillary GC analysis (ISO 190 °C, t_R = 13.81 (cis isomer), 14.94 (trans isomer)): ^{1}H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 6.6 Hz), 1.70 (9 H, s), 3.78 (3 H, s), 4.08–4.43 (1 H, m), 5.15 (1 H, d, J = 5.3 Hz), 5.60 (1 H, d, J = 5.8 Hz), 6.22 (1 H, d, J = 15.8 Hz), 6.93 (1 H, dd, J = 15.8 Hz, J = 5.8 Hz), 7.30 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 16.0, 28.4, 51.6, 55.7, 80.7, 81.6, 86.1, 144.1, 152.4, 166.3; IR ($CHCl_3$) ν 2980, 1700, 1400, 1360, 1165 cm^{-1}; $[\alpha]^{25}_D$ −81.1° (c 1.7, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.60; H, 7.23; N, 4.10.

***cis*-3Dc**: purified by flash chromatography (hexane/AcOEt, 75:25); ^{1}H NMR ($CDCl_3$) δ 0.79 (3 H, d, J = 6.6 Hz), 3.72 (3 H, s), 3.78 (3 H, s), 4.15–4.48 (1 H, m), 5.13 (1 H, d, J = 5.3 Hz), 5.66 (1 H, d, J = 5.6 Hz), 6.25 (1 H, d, J = 16.0 Hz), 6.98 (1 H, dd, J = 16.0 Hz, J = 5.6 Hz), 7.31 (5 H, s). Anal. Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.93; H, 6.30; N, 4.61.

8. The diastereomeric ratio was determined by capillary GC analysis (ISO 240 °C, t_R = 9.37 (cis isomer), 8.85 (trans isomer)). The crude product was purified by flash chromatography (hexane/AcOEt, 80:20).

***cis*-8**: ^{1}H NMR ($CDCl_3$) δ 1.40 (3 H, d, J = 6.5 Hz), 3.70 (3 H, s), 3.78 (1 H, dq, J = 6.5 Hz, J = 7.5 Hz), 4.58 (1 H, d, J = 7.5 Hz), 4.95–5.28 (2 H, m), 5.68 (1 H, dd, J = 0.5 Hz, J = 7.0 Hz), 6.12 (1 H, dd, J = 16.0 Hz, J = 0.5 Hz), 6.95 (1 H, dd, J = 16.0 Hz, J = 7.0 Hz), 7.32 (5 H, s), 7.38 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 16.1, 51.7, 59.2, 67.2, 87.1, 87.2, 124.6, 143.0, 152.4, 166.1. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.30; H, 6.08; N, 3.66.

***trans*-8**: ^{1}H NMR ($CDCl_3$) δ 1.40 (3 H, d, J = 6.5 Hz), 3.75 (3 H, s), 3.85 (1 H, dq, J = 6.5 Hz, J = 7.5 Hz), 4.75 (1 H, d, J = 7.5 Hz), 5.18 (2 H, s), 6.0 (1 H, dd, J = 0.5 Hz, J = 5.0 Hz), 6.12 (1 H, dd, J = 16.0 Hz, J = 0.5 Hz), 6.95 (1 H, dd, J =16.0 Hz, J = 5.0 Hz), 7.35 (10 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 18.0, 51.8, 59.6, 67.5, 85.9, 87.3, 123.1, 143.4, 166.3. Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.25; H, 6.10; N, 3.69.

Intermediates 4b. To a 0.5 M C_6H_6 solution of acetal **2b** (1.5 equiv) and **1A** (1 equiv) were added pyridinium tosylate (0.3 equiv) and molecular sieves, 4 Å. The mixture was stirred for 40 h at room temperature, then diluted with AcOEt, washed with water, dried over Na_2SO_4, and filtered and the solvent evaporated under reduced pressure (without heating). The crude product was purified by preparative TLC (hexane/AcOEt, 80:20) (34% yield) (partial conversion). The acetals **4b** were obtained in 4:1 diastereomeric ratio (checked by ^{1}H and ^{13}C NMR analyses): ^{1}H NMR ($CDCl_3$) δ 1.00 (3 H, d, J = 6.8 Hz), 1.66 (3 H, dd, J = 1.0 Hz, J = 6.0 Hz, minor) and 1.73 (3 H, dd, J = 6.0 Hz, J = 1.0 Hz), 3.17 (3 H, s) and 3.30 (3 H, s, minor), 3.96 (1 H, ddq, J = 6.8 Hz, J = 8.8 Hz, J = 3.5 Hz), 4.67 (1 H, dq, J = 1.0 Hz, J = 4.8 Hz), 4.67 (1 H, d, J = 8.8 Hz), 4.89 (1 H, d, J = 3.5 Hz), 5.13 (2 H, s), 5.46 (1 H, ddq, J = 16.0 Hz, J = 4.8 Hz, J = 1.0 Hz), 5.81 (1 H, dq, J = 16.0 Hz, J = 6.0 Hz), 7.3 (10 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 14.2, 14.4, 17.4 (minor) and 17.5, 51.9 and 54.5 (minor), 66.5 and 66.8 (minor), 79.1 (minor) and 79.7, 79.0 (minor) and 100.3, 103.4 (minor) and 103.8; IR ($CHCl_3$) ν 3440, 2830, 2820, 1710, 1510 cm^{-1}.

Intermediates 4c. To a 0.5 M C_6H_6 solution of dimethyl acetal **2c** (1 equiv) and **1A** (1.5 equiv) was added pyridinium tosylate (0.3 equiv). The mixture was stirred for 48 h at 65–70 °C and then worked up as reported for **4b**. The crude product was purified by flash chromatography (hexane/AcOEt, 80:20). ^{1}H NMR and ^{13}C NMR analyses revealed a 3:1 diastereomeric ratio: ^{1}H NMR (C_6D_6/50 °C) δ 0.80 (3 H, d, J = 7.0 Hz, minor) and 0.88 (3 H, d, J = 6.5 Hz), 2.93 (3 H, s) and 2.95 (3 H, s, minor), 3.37 (3 H, s, minor) and 3.41 (3 H, s), 4.10 (1 H, ddq, J = 6.5 Hz, J = 3.4 Hz, J = 9.0 Hz), 4.55 (1 H, br d, J = 9.0 Hz), 4.75 (1 H, dd, J = 4.3 Hz, J = 1.0 Hz), 4.82 (1 H, d, minor) and 4.96 (1 H, d, J = 3.4 Hz), 5.12 (2 H, s), 6.20 (1 H, dd, J = 16.0 Hz, J = 1.0 Hz), 6.95 (1 H, dd, J = 16.0 Hz, J = 4.3 Hz), 7.20 (10 H, br s); ^{13}C NMR ($CDCl_3$/40 °C) selected data δ 14.4 and 14.8 (minor), 51.7 and 51.9 (minor), 52.0 and 54.0 (minor), 66.6, 80.0, 80.2, 97.8 and 101.1 (minor), 142.6 (minor) and 142.8, 155.6, 166.0 (minor) and 166.2; IR ($CHCl_3$) ν 3450, 1725, 1510 cm^{-1}.

Preparation of R_2CuLi Species. Me_2CuLi was prepared by MeLi (3 mmol, 1.5 M in Et_2O) addition to a suspension of CuI (1.5 mmol) in dry Et_2O (3 mL) at 0 °C and subsequent stirring for 10 min.

Et_2CuLi was prepared by EtLi addition (3 mmol, 0.27 M in pentane) to a suspension of CuI (1.5 mmol) in dry Et_2O (3 mL) at −30 °C and subsequent stirring for 10 min.

Bu_2CuLi was prepared by BuLi addition (3 mmol, 1.5 M in hexane) to a suspension of CuI (1.5 mmol) in dry Et_2O (3 mL) at −25 °C and subsequent stirring for 10 min.

Cuprate Additions to Oxazolidine 3Ac. Synthesis of Oxazolidines 9a–c. To a solution of R_2CuLi (1.5 mmol) (obtained as above reported) at −25 °C was added the oxazolidine *cis*-**3Ac** (1 mmol) dissolved in dry Et_2O (1 mL). After 30 min at −25 °C, the mixture was treated with an NH_3/NH_4Cl pH 8 buffer solution and then stirred at room temperature for 15 min. After Et_2O extraction, the organic layers were dried over Na_2SO_4 and filtered and the solvent was evaporated under reduced pressure. The crude products were checked by ^1H and ^{13}C NMR analyses in order to determine the diastereomeric ratios (≥95:5) and then purified by flash chromatography (hexane/AcOEt, 80:20): yield 70–72%. In order to avoid line broadening due to carbamate isomerism, we recorded the ^{13}C NMR spectra at 45 °C.

9a was also prepared as above but by TMSCl (3 molar equiv) addition at −78 °C prior to the substrate addition: diastereomeric ratio ≥95:5; yield 72%; ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 6.4 Hz), 1.15 (3 H, d, J = 7.1 Hz), 2.10–3.15 (3 H, m), 3.67 (3 H, s), 4.30 (1 H, dq, J = 6.4 Hz, J = 6.7 Hz), 5.02 (1 H, d, J = 6.7 Hz), 5.15 (1 H, d, J = 3.0 Hz), 5.20 (2 H, s), 7.30 (5 H, s), 7.35 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 16.2, 16.4, 33.0, 34.9, 51.4, 56.5, 67.1, 80.6, 92.1, 154.1, 173.2; IR ($CHCl_3$) ν 1735, 1700, 1605, 1455, 1415 cm^{-1}. Anal. Calcd for $C_{23}H_{27}NO_5$: C, 69.50; H, 6.85; N, 3.52. Found: C, 69.52; H, 6.86; N, 3.51.

9b: ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.7 Hz), 0.85 (3 H, t, J = 5.3 Hz), 1.20–1.75 (6 H, m), 2.15–3.10 (3 H, m), 3.65 (3 H, s), 4.30 (1 H, dq, J = 6.4 Hz, J = 6.7 Hz), 5.05 (1 H, d, J = 6.7 Hz), 5.18 (2 H, s), 5.22 (1 H, d, J = 2.0 Hz), 7.30 (5 H, s), 7.40 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 13.9, 16.3, 22.7, 29.1, 30.8, 33.5, 37.0, 51.3, 56.5, 67.1, 80.6, 90.5, 154.0, 173.4; IR ($CHCl_3$) ν 1725, 1690, 1600, 1490, 1405, 1340 cm^{-1}. Anal. Calcd for $C_{26}H_{33}NO_5$: C, 71.05; H, 7.57; N, 3.19. Found: C, 71.12; H, 7.45; N, 3.23.

9c: ^1H NMR ($CDCl_3$) δ 0.78 (3 H, d, J = 6.4 Hz), 1.00 (3 H, t, J = 6.7 Hz), 1.60 (2 H, m), 2.15–2.90 (3 H, m), 3.65 (3 H, s), 4.28 (1 H, dq, J = 6.4 Hz, J = 6.7 Hz), 5.05 (1 H, d, J = 6.7 Hz), 5.15 (2 H, s), 5.25 (1 H, d, J = 3.0 Hz), 7.30 (5 H, s), 7.38 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 11.7, 16.4, 24.1, 33.2, 38.7, 51.5, 56.4, 67.2, 80.6, 90.5, 154.2, 173.8; IR ($CHCl_3$) ν 1735, 1700, 1610, 1500, 1415, 1350 cm^{-1}. Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.04; H, 7.12; N, 3.41.

Synthesis of 9e via $(CH_2CH)_2CuLi$. To a suspension of CuBr·Me_2S (freshly crystallized) (514 mg, 2.5 mmol) in dry Et_2O (3.4 mL) and Me_2S (2.5 mL) at −60 °C was added vinyllithium[27] (10 mL, 0.5 M in Et_2O), and after 10 min, oxazolidine *cis*-**3Ac** (1.25 mmol) dissolved in Et_2O (2 mL) was added. The mixture was stirred at −50 °C for 40 min, then quenched with a pH 8 buffer solution (NH_3/NH_4Cl), and worked up as usual. Diastereomeric ratio (≥95:5) was determined by ^1H and ^{13}C NMR. The crude product was purified by flash chromatography (hexane/AcOEt, 85:15): yield 75%; ^1H NMR ($CDCl_3$) δ 0.82 (3 H, d, J = 7.0 Hz), 2.45–2.75 (2 H, m), 3.30–3.60 (1 H, m), 3.65 (3 H, s), 4.20–4.40 (1 H, m), 5.05 (1 H, d, J = 6.0 Hz), 5.20 (2 H, s), 5.10–5.30 (3 H, m), 5.80–6.05 (1 H, m), 7.27–7.40 (10 H, m); ^{13}C NMR ($CDCl_3$/45 °C) selected data δ 16.4, 33.3, 43.3, 51.6, 56.3, 67.3, 80.8, 91.1, 118.0, 136.6, 154.1, 172.8; IR ($CHCl_3$) ν 1740, 1705, 1645, 1610, 1500, 1420, 1350 cm^{-1}. Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42. Found: C, 70.35; H, 6.50; N, 3.40.

Synthesis of 9e via $CH_2CHMgBr/CuI$. To a suspension of CuI (1.69 mmol, 322.5 mg) in THF (5.6 mL) was slowly added a 2.1 M THF $CH_2CHMgBr$ solution (0.806 mL) at −40 °C. After 5 min at −35 °C, the reaction mixture was cooled to −78 °C and *cis*-**3Ac** (0.56 mmol, 215 mg) dissolved in the minimum amount of THF was added. The mixture was stirred for 30 min and then quenched as described previously: diastereomeric ratio ≥95:5 (71% yield).

Reduction of 9e to 9c. 9e (0.9 mmol) in THF (9 mL) was hydrogenated (1 atm of H_2) in the presence of 5% rhodium/alumina for 30 min at room temperature. The crude reaction mixture was filtered and the solvent evaporated to give **9c**, which was purified by flash chromatography (hexane/AcOEt, 80:20) (97% yield).

Synthesis of 9f. Allyllithium (2.7 mmol, 1 M in Et_2O), obtained according to ref 28, was diluted with Et_2O (1.5 mL). After cooling to −78 °C, CuBr·Me_2S (1.35 mmol), dissolved in Me_2S (2 mL), was added. After the mixture was stirred for a further 45 min, oxazolidine *cis*-**3Ac** (1 mmol) dissolved in THF (2 mL) was added. After slowly warming to 25 °C, the reaction mixture was quenched and worked up as reported above. The diastereomeric ratio (89:11) was determined by ^1H and ^{13}C NMR. The crude product was purified by flash chromatography (hexane/AcOEt, 80:20) (54% yield): ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.7 Hz), 2.15–2.65 (4 H, m), 2.75–3.30 (1 H, m), 3.70 (3 H, s), 4.30 (1 H, dq, J = 6.7 Hz, J = 6.0 Hz), 5.05 (1 H, d, J = 6.0 Hz), 5.00–5.15 (2 H, m), 5.20 (2 H, s), 5.25 (1 H, d, J = 3.0 Hz), 5.45–6.15 (1 H, m), 7.30 (5 H, s), 7.35 (5 H, s); ^{13}C NMR ($CDCl_3$/45 °C) selected data δ 16.3, 32.9, 35.5, 37.0, 37.5 (minor), 51.3, 56.6, 67.2, 80.7, 90.5, 90.7 (minor), 116.8, 136.0, 154.2, 173.3. Anal. Calcd for $C_{25}H_{29}NO_5$: C, 70.90; H, 6.90; N, 3.31. Found: C, 70.95; H, 6.85; N, 3.40.

Reduction of 9f to 9d. The hydrogenation of oxazolidine **9f** was performed as reported for **9e**. The crude product was purified by flash chromatography (benzene/Et_2O, 95:5), affording pure **9d** (90% yield): ^1H NMR ($CDCl_3$) δ 0.80 (3 H, d, J = 6.7 Hz), 0.87 (3 H, br t), 1.25–1.75 (4 H, m), 2.10–2.90 (3 H, m), 3.65 (3 H, s), 4.25 (1 H, dq, J = 6.7 Hz, J = 6.0 Hz), 5.05 (1 H, d, J = 6.0 Hz), 5.15 (2 H, s), 5.20 (1 H, d, J = 3.0 Hz), 7.30 (5 H, s), 7.35 (5 H, s). Anal. Calcd for $C_{25}H_{31}NO_5$: C, 70.57; H, 7.34; N, 3.29. Found: C, 70.53; H, 7.40; N, 3.21.

Synthesis of Aldehydes 11a–d. General Procedure. To a solution of oxazolidine **10a–d** (1 mmol) in dry CH_2Cl_2 (8 mL) were added 1,2-ethanedithiol (10 mmol) and BF_3·Et_2O (0.4 mmol), and the reaction mixture was allowed to stand for 15 h at room temperature. The mixture was quenched with a 5% aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and filtered, and the solvent was evaporated. The crude reaction mixture, dissolved in acetone/water, 4:1 (2 mL), and treated with $CaCO_3$ (3 mmol) and MeI (10 mmol), was stirred for 12 h at 60 °C. The resulting mixture was filtered on a Celite pad. The filtrate was washed with a 5 M $AcONH_4$ solution and then with brine, dried, and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography. Enantiomeric excesses were determined by 200-MHz ^1H NMR by using Eu(hfc)$_3$ as shift reagent.

11a: flash chromatography (petroleum ether/Et_2O, 75:25) (85% yield); ^1H NMR ($CDCl_3$) δ 1.20 (3 H, d, J = 6.7 Hz), 2.25–3.00 (3 H, m), 3.70 (3 H, s), 9.70 (1 H, d, J = 0.3 Hz); $[\alpha]^{25}_D$ −71.2° (c 1.0, Et_2O); 93% ee.

11b: flash chromatography (hexane/AcOEt, 88:12) (80% yield); ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t, J = 6.7 Hz), 1.15–1.90 (6 H, m), 2.20–2.95 (3 H, m), 3.70 (3 H, s), 9.70 (1 H, d, J = 0.3 Hz); $[\alpha]^{25}_D$ −68.5° (c 1.0, Et_2O); 91% ee.

11c: flash chromatography (hexane/AcOEt, 80:20) (84% yield); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 7.5 Hz), 1.40–1.80 (2 H, m), 2.15–2.95 (3 H, m), 3.68 (3 H, s), 9.70 (1 H, d, J = 0.3 Hz); $[\alpha]^{25}_D$ −69.8° (c 1.0, Et_2O); 90% ee.

11d: flash chromatography (hexane/AcOEt, 80:20) (82% yield); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t, J = 6.5 Hz), 1.25–1.70 (4 H, m), 2.25–2.95 (3 H, m), 3.65 (3 H, s), 9.70 (1 H, d, J = 0.3 Hz); $[\alpha]^{25}_D$ −58.4° (c 1.0, Et_2O); 78% ee.

Reduction of 11a to (2*S*)-2-Methylbutane-1,4-diol. Aldehyde **11a** (1 mmol) dissolved in Et_2O (6 mL) was added to $LiAlH_4$ (70 mg) in Et_2O (3 mL) at 0 °C. After 20 min of stirring, the mixture was quenched and worked up.[29] The crude product was purified by flash chromatography (AcOEt/2% MeOH): yield

(27) Vinyllithium was prepared from tetravinyltin (see: Seyferth, D.; Weiner, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 3583) and butyllithium (see: Seyferth, D.; Stone, F. G. A. *J. Am. Chem. Soc.* **1957**, *79*, 515).

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60%; $[\alpha]^{25}_D$ −13.4° (c 0.7, MeOH);[24] ^{1}H NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 6.0 Hz), 1.40–2.00 (3 H, m), 2.15 (2 H, br s), 3.30–3.90 (4 H, m).

Synthesis of 10. This compound was synthesized by starting from *cis*-**3Dc** as reported above for *cis*-**3Ac**. The diastereomeric ratio has been obtained by capillary GC analysis (150 °C 0 min/4 °C/min/250 °C 5 min, t_R = 13.72 (major), 14.10 (minor)). The yield is reported in Table II: ^{1}H NMR ($CDCl_3$) δ 0.77 (3 H, d, J = 7.1 Hz), 1.16 (3 H, d, J = 7.0 Hz), 2.10–2.90 (3 H, m), 3.67 (3 H, s), 3.73 (3 H, s), 4.10–4.33 (1 H, m), 5.02 (1 H, d, J = 5.9 Hz), 5.09 (1 H, d, J = 2.4 Hz), 7.3 (5 H, s); ^{13}C NMR ($CDCl_3$) selected data δ 16.2, 16.4, 33.0, 34.9, 51.5, 52.5, 56.5, 80.7, 92.2, 155.0, 173.6. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.55; H, 7.24; N, 4.38.

The same product was obtained by adding Bu_3P (1 equiv, entry 2, Table II or 4 equiv, entry 3, Table II) prior to **3Dc** addition.

An analytical sample of **10** as a 1:1 $C_{1'}$ epimeric mixture has been obtained via hydrogenation of methyl 4,4-dimethoxy-3-methylcrotonate (E:Z = 6:4) (H_2, 1 atm, Pd/C, MeOH) and subsequent BF_3·Et_2O-catalyzed cyclization with excess **1D**: ^{1}H NMR ($CDCl_3$) δ 1.03 (3 H, d, J = 6.6 Hz, $C_{1'}$-Me *R* isomer), 1.16 (3 H, d, J = 7.0 Hz, $C_{1'}$-Me *S* isomer); ^{13}C NMR ($CDCl_3$) selected data δ 91.3 (*R* isomer) and 92.2 (S isomer).

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Registry No. 1A, 104863-92-5; **1B**, 108591-33-9; **1C**, 113322-99-9; **1D**, 113323-00-5; **2a**, 6044-68-4; **2b**, 18318-79-1; **2c**, 32815-00-2; *cis*-**3Aa**, 113323-06-1; *trans*-**3Aa**, 113323-07-2; *cis*-**3Ab**, 113427-44-4; *trans*-**3Ab**, 113427-45-5; *cis*-**3Ac**, 105226-55-9; *trans*-**3Ac**, 113427-46-6; *cis*-**3Bb**, 113323-04-9; *trans*-**3Bb**, 113323-05-0; *cis*-**3Bc**, 113323-08-3; *trans*-**3Bc**, 113323-09-4; *cis*-**3Cc**, 113323-02-7; *trans*-**3Cc**, 113323-03-8; *cis*-**3Dc**, 113323-10-7; *trans*-**3Dc**, 113351-82-9; **4b** (isomer 1), 113323-11-8; **4b** (isomer 2), 113427-49-9; **4c** (isomer 1), 113323-12-9; **4c** (isomer 2), 113427-50-2; **7**, 113323-01-6; *cis*-**8**, 113427-47-7; *trans*-**8**, 113427-48-8; **9a** (isomer 1), 105140-27-0; **9a** (isomer 2), 113323-13-0; **9b**, 105140-28-1; **9c**, 105140-29-2; **9d**, 105140-32-7; **9e** (isomer 1), 105140-30-5; **9e** (isomer 2), 113323-14-1; **9f** (isomer 1), 105140-31-6; **9f** (isomer 2), 113323-15-2; **10a**, 113351-83-0; **10b**, 113351-65-8; **10c** (isomer 1), 113323-16-3; **10c** (isomer 2), 113323-18-5; **10d**, 113323-17-4; **11a**, 105226-56-0; **11b**, 71633-61-9; **11c**, 71464-83-0; **11d**, 71464-84-1; (2*S*)-2-methylbutane-1,4-diol, 70423-38-0.

Supplementary Material Available: Tables of atomic coordinates, anisotropic thermal parameters, bond distances, and bond angles (5 pages). Ordering information is given on any current masthead page.

Chemoenzymic Synthesis of Chiral Furan Derivatives: Useful Building Blocks for Optically Active Structures

Dale G. Drueckhammer, Carlos F. Barbas III, Kenji Nozaki, and Chi-Huey Wong*

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Cynthia Y. Wood and Marco A. Ciufolini*

Department of Chemistry, Rice University, Houston, Texas 77251

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Practical procedures have been developed for the enantioselective reduction of 2-acetylfuran (**6a**) and 2-(trifluoroacetyl)furan (**6b**) to the corresponding carbinols (*S*)-**1** and **7b** with 88–90% ee using *Thermoanaerobium brockii* alcohol dehydrogenase coupled with an NADPH regeneration system. Kinetic resolution of racemic (*S*)-**1** via lipase-catalyzed esterification, followed by cholesterol esterase or lipase-catalyzed hydrolysis of the ester gives (*R*)-**1** with 94% ee. Conversion of (*S*)-**1** to the dihydropyranones **4** and **5** without racemization has been illustrated. Enantioselective hydrolysis of N-protected furylglycine methyl esters catalyzed by papain gave the unreacted esters and the free acids (*S* form) both in 45% yield and 97% ee. The resolved furylglycines are excellent substrates for the synthesis of optically active synthons for alkaloids.

Introduction

A strategy for the total synthesis of monosaccharides involves the preparation of a properly substituted furylcarbinol as a building block.[1-3] In most cases, however, a racemic carbinol is used as starting material. If an optically active furylcarbinol such as (*S*)-**1** were available, it would be useful for the synthesis of the L series of dihydropyranones (Figure 1), which would serve subsequently as substrates for the facile introduction of further functionality.[1c] We report here several preparative enzymatic routes to (*R*)- and (*S*)-furylmethylcarbinols and (*R*)-furyl(trifluoromethyl)carbinol through an asymmetric reduction of the corresponding acylfuran catalyzed by the alcohol dehydrogenase from *Thermoanaerobium brockii* (TADH)[4] and through a kinetic resolution of the racemic carbinol esters catalyzed by esterases. Compound (*S*)-**1** was converted to the 2,3,6-trideoxy-L-hex-2-enopyranosid-4-uloses (**4** and **5**) to illustrate the synthetic utility. We also report a practical procedure for the preparation of optically active (>97% ee) furylglycine derivatives such as (*S*)- and (*R*)-**9** (X = benzoyl; COOBn;

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