Regio- and Stereocontrolled Formation of Chiral Epoxy Oxazolidines via Bromocarbamation of *N*-Boc Alkenyl Oxazolidines. Application to Asymmetric Synthesis

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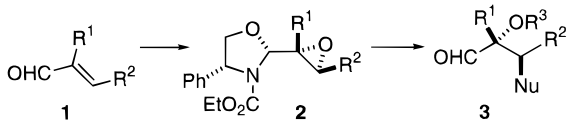
Treatment of α-alkenyl *N*-Boc oxazolidines with *N*-bromosuccinimide leads to epoxy oxazolidines via a bromocyclocarbamation reaction which is completely stereoselective. Action of sodium azide on these epoxides, followed by a few functional group manipulations, eventually affords chiral *β*-amino alcohols which are intermediates for the enantioselective synthesis of bioactive products: the *anti* side chain of taxol and a hydroxyethylamine isostere. Both the bromocarbamation cyclization and the nucleophilic cleavage of epoxides are totally regioselective. AM1 calculations suggest that this selectivity is controlled by the positive charge distribution at the electrophilic centers.

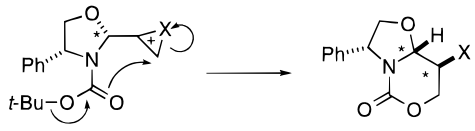
Oxazolidine moieties are easily synthesized from enantiomerically pure *β*-amino alcohols and are widely recognized as very useful chiral auxiliaries for several asymmetric reactions.[1] On the other hand, chiral epoxides have frequently been involved in the design of strategies for the achievement of stereocontrol.[2] In this respect, it is surprising to note that only one example[3] is known reporting the combined influence in the same substrate of both epoxide and oxazolidine moieties. This fact can be ascribed to the instability[4] of epoxy aldehydes which would otherwise constitute obvious materials for the direct formation of such oxazolidines.

We wish to report a full account[5] of new methodology which allows the preparation of enantiopure epoxy oxazolidines **2** from α,*β*-unsaturated aldehydes **1**. Nucleophilic attack on these epoxides occurs in a totally regio- and stereoselective manner and eventually leads to aldehydes **3**. This sequence of reactions creates two contiguous stereocenters, thus offering a new method for enantioselective synthesis.



The key step of this transformation is a fully regio- and stereoselective halocyclization process involving the oxazolidine *N*-Boc substituent. In this reaction (Scheme 1) a bridged halonium ion is attacked by the carbamate moiety which acts as a nucleophile.[6] This process features 1,2-stereoinduction directed by the C-2 oxazolidine center, in agreement with other examples of such stereoselective halocyclizations.[7] Completion of the synthesis of the modified aldehydes **3** only requires a few straightforward functional group manipulations.

Scheme 1



As exemplified below, epoxy oxazolidines synthesized in this way were used for the enantioselective synthesis of compounds of biological interest that contain a *β*-amino alcohol moiety. Moreover theoretical calculations were performed in order to explain the complete regioselectivity which was observed during nucleophilic attack on both the bridged halonium ion and the epoxy oxazolidines.

Results and Discussion

Synthesis of α-Epoxy Oxazolidines. Condensation of α,*β*-ethylenic aldehydes **4a**−**f** and **4g** with (*R*)- and (*S*)-

[⊗] Abstract published in *Advance ACS Abstracts,* March 1, 1997.

(1) For some recent examples, see: (a) Meyers, A. I.; Seefeld, M. A.; Lefker, B. A. *J. Org. Chem.* **1996**, *61*, 5712−5713. (b) Andrews, M. D.; Brewster, A. G.; Moloney, M. G. Synlett 1996, 612−614. (c) Roth, G. P.; Leonard, S. F.; Tong, L. *J. Org. Chem.* **1996**, *61*, 5710−5711. (d) Amat, M.; Llor, N.; Hidalgo, J.; Bosch, J.; Molins, E.; Miravittles, C. *Tetrahedron: Asymmetry* **1996**, *7*, 2501−2504. (e) Froelich, O.; Desos, P.; Bonin, M.; Quirion, J. C.; Husson, H. P.; Zhu, J. *J. Org. Chem.* **1996**, *61*, 6700−6705. (f) Garcia-Valverde, M.; Pedrosa, R.; Vicente, M.; Garcia-Granda, S.; Guttierez-Rodriguez, A. *Tetrahedron* **1996**, *52*, 10761−10770. (g) O'Brien, P.; Warren, S. *Tetrahedron Lett.* **1996**, *37*, 3051−3054. (h) Agami, C.; Mathieu, H.; Couty, F. *Tetrahedron Lett.* **1996**, *37*, 4001−4002.

(2) Nicolaou, K. C.; Sorensen, E. J. *Classics in Total Synthesis*; VCH: New York, 1996.

(3) Cardani, S.; Gennari, C.; Scolastico, C.; Villa, R. *Tetrahedron* **1989**, *45*, 7397−7404.

(4) Behrens, C. H.; Sharpless, K. B. *J. Org. Chem.* **1985**, *50*, 5696−5704.

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(6) For other examples related to nucleophilic reactivity of carbamate moieties, see: (a) Agami, C.; Couty, F.; Hamon, L.; Venier, O. *Tetrahedron Lett.* **1993**, *34*, 4509−4512. (b) Curran, T. P.; Pollastri, M. P.; Abelleira, S. M.; Messier, R. J.; McCollum, T. A. *Tetrahedron Lett.* **1994**, *35*, 5409−5412. (c) Campanini, L.; Duréault, A.; Depezay, J. C. *Tetrahedron Lett.* **1995**, *36*, 8015−8018. (d) Vanucci, C.; Brusson, X.; Verdel, V.; Zana, F.; Dhimane, H.; Lhommet, G. *Tetrahedron Lett.* **1995**, *36*, 2971−2974. (d) Haddad, M.; Larcheveque, M. *Tetrahedron Lett.* **1996**, *37*, 4525−4528. (e) Lee, J. W.; Lee, J. H.; Son, H. J.; Choi, Y. K.; Yoon, G. J.; Park, M. H. *Synth. Commun.* **1996**, *26*, 83−88. (f) Sepulveda-Arques, J.; Armero-Alarte, T.; Acero-Alarcon, A.; Zaballos-Garcia, E.; Solesio, B. Y.; Carrera, J. E. *Tetrahedron* **1996**, *52*, 2097−2102. (g) Williams, L.; Zhang, Z.; Shao, F.; Caroll, F. J.; Joullié, M. M. *Tetrahedron* **1996**, *52*, 11673−11694.

(7) For examples of 1,2-stereoinduction in this field, see: (a) Parker, K. A.; O'Fee, R. *J. Am. Chem. Soc.* **1983**, *105*, 654−655. (b) Kobayashi, S.; Tashiyuki, I.; Ohno, M. *Tetrahedron Lett.* **1984**, *25*, 5079−5082. (c) Kamiyama, K.; Urano, Y.; Kobayashi, S.; Ohno, M. *Tetrahedron Lett.* **1987**, *28*, 3123−3126. (d) Pauls, H. W.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1980**, *102*, 3956−3957. (e) Guindon, Y.; Siassi, A.; Ghiro, E.; Bantle, G.; Jung, G. *Tetrahedron Lett.* **1992**, *33*, 4257−4260. (f) Guindon, Y.; Slassi, A.; Rancourt, J.; Bantle, G.; Bencheqroun, M.; Murtagh, L.; Ghiro, E.; Jung, G. *J. Org. Chem.* **1995**, *60*, 288−289.

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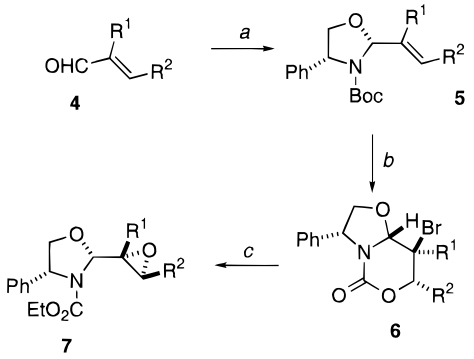
Scheme 2[a]



	R1	R2	yields (%) 5	6	7
a	H	Ph	93	80	72
b	Me	Ph	62	90	85
c	H	Me	57	53[c]	80
d	Me	Et	80	73	71
e	H	MeCH=CH-	80	80	80
f	H	Pr	81	77[c]	68[d]
g	H	$PhCH_2$	60[b]	92[b]	97[b]

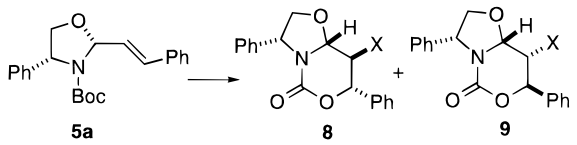
[a] Reaction conditions: (a) (*R*)-phenylglycinol, 4 Å molecular sieves, then $(Boc)_2O$; (b) NBS, DME−H_2O; (c) NaOEt, EtOH. [b] Respectively for *ent*-**5g**, *ent*-**6g**, and *ent*-**7g** from (*S*)-phenylglycinol). [c] Overall yield from **4**. [d] Overall yield from **5f**.

Table 1. Halocyclization of Oxazolidine 5a

entry	conditions	**8**/**9**[a]	yield,%[b]
1	Br_2, CH_2Cl_2, 0 °C	66/34	77
2	Br_2, CH_2Cl_2, −70 °C	80/20	80
3	I_2, CH_2Cl_2, 20 °C	100/0	35
4	NBS, DME−H_2O, 20 °C	100/0	80

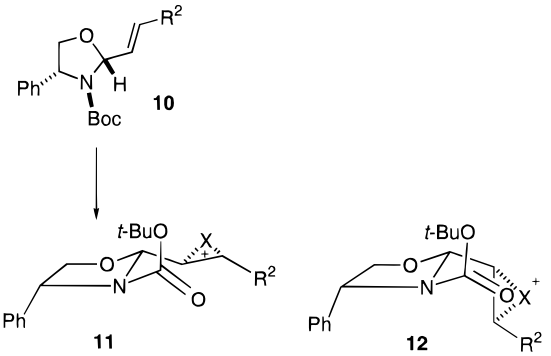
[a] Ratio determined by ^1H NMR on the crude reaction mixture. [b] Isolated yields.

phenylglycinol, respectively, in the presence of di-*tert*-butyl dicarbonate (Boc_2O), afforded alkenyl oxazolidines **5a**−**g** (Scheme 2). In all cases, 2,4-*cis*-disubstituted oxazolidines were produced in agreement with the well known stereoselectivity exhibited by such condensations.[8]



The action of *N*-bromosuccinimide on compounds **5a**−**g** effected the cyclization step[9] affording products **6a**−**g**. Table 1 shows the variation of the ratio of products **8** and **9** obtained from **5a** with various halogenating reagents. *N*-Bromosuccinimide reacted very suitably with all alkenyl oxazolidines **5a**−**g** as regards reactivity as well as stereoselectivity. Bromine was reversibly added to the ethylenic diastereoface that is opposite to the urethane moiety in order for the transient bromonium ion to be intercepted by this group. The complete diastereoselectivity that is displayed by this bromocarbamation reaction can be rationalized on a conformational basis. The intermediate bridged bromonium ion can be depicted either as structure **11** or **12**, depending on which ethylenic double bond diastereoface was concerned. Actually, the stereoselectivity which was observed in the cyclized products **6a**−**g** corresponds to the involvement of structure **11**. Diasteromeric intermediates **11** and **12** show a *trans* geometry between the bulky *N*-Boc group and both the phenyl and the side-chain substituents; compared with its diastereomer **12**, reactive species **11** fulfills an important requirement: the arrangement of the reactive centers in **11** leads to a chair cyclization transition state.

Moreover we have to consider the possibility that not only is **11** the reactive species but that it might also have been produced in preference to **12**. In fact, Danishefsky et al.[10] suggested that, when reacting with an electrophilic reagent, the ethylenic double bond of propenyl groups linked to pyranosides adopts a coplanar *s-cis* conformation with respect to a C−O heterocycle bond. This geometry would favor the stabilization of the incipient positive charge by the C−O dipole. In the present case, should conformation **10** of the alkenyl oxazolidine be the reactive one, in agreement with the Danishefsky hypothesis, formation of the bridged halonium ion would have indeed occurred on the less hindered diastereoface (i.e. *anti* to the *N*-Boc group) leading to stereoisomer **11**. It is worth mentioning that the stereoselectivity of dihydroxylation of alkenyl oxazolidines was already explained by Colombo et al.[11] on the basis of an analogous C=C−C=O *s-cis* arrangement.



In addition, this cyclization was totally regioselective, the preferred pathway being a 6-*endo* and not a 5-*exo* process. This selectivity is discussed since it can be related to the regioselective nucleophilic opening of epoxides **7** (*vide infra*).

As shown in Scheme 2, epoxy oxazolidines **7a**−**g** were produced from the action of sodium ethoxide on the corresponding bromo oxazinones **6a**−**g**. A base-induced cleavage of the cyclic carbamate moiety gives rise to an intramolecular substitution of bromine leading to the sterospecific formation of the epoxide group.

Synthesis of chiral *β*-Amino Alcohols. From epoxides **7a** and *ent*-**7g** two series of reactions were achieved with the aim of synthesizing two compounds of biological interest. On the other hand, these transformations provide chemical correlations in order to confirm the configurations of the starting epoxides.

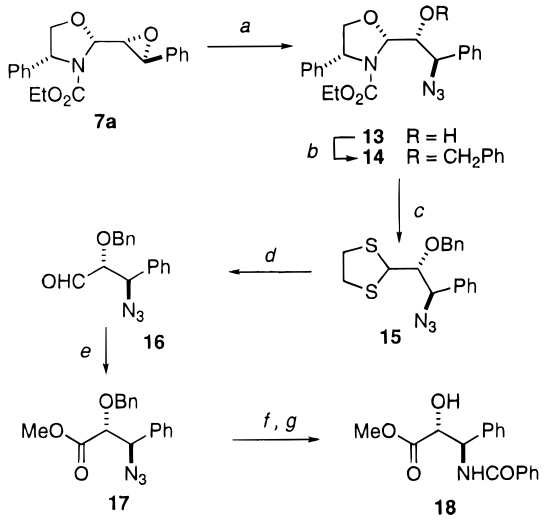
(8) (a) Agami, C.; Rizk, T. *Tetrahedron* **1985**, *41*, 537−540. (b) Arsenyadis, S.; Huang, P. Q.; Molleret, N.; Beloeil, J. C.; Husson, H. P. *Heterocycles* **1990**, *31*, 1789−1799. (c) Prien, O.; Hoffmann, H.; Conde-Frieboes, K.; Krettek, T.; Berger, B.; Wagner, K.; Bolte, M.; Hoppe, D. *Synthesis* **1994**, 1313−1321. (d) Higashiyama, K.; Nakagawa, K.; Takahashi, H. *Heterocycles* **1995**, *41*, 2007−2017.

(9) For an excellent review on halocyclocarbamation and related cyclizations including halolactonization, see: Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321−3408.

(10) Danishefsky, S. J.; Larson, E.; Springer, J. P. *J. Am. Chem. Soc.* **1985**, *107*, 1274−1280. See also: Stork, G.; Kahn, M. *Tetrahedron Lett.* **1983**, *24*, 3951−3954.

(11) Colombo, L.; Gennari, C.; Poli, G.; Scolastico, C. *Tetrahedron Lett.* **1985**, *26*, 5459−5462.

Scheme 3[a]



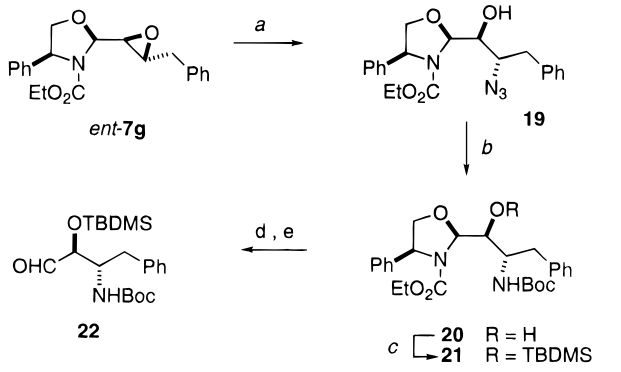
[a] Reaction conditions: (a) NaN_3, NH_4Cl, EtOH, reflux; (b) NaH, $PhCH_2Br$, DMF, rt (71% from **7a**); (c) $HSCH_2CH_2SH$, $Et_2O{-}BF_3$, CH_2Cl_2, reflux (73%); (d) $CaCO_3$, MeI, acetone:H_2O (4:1), 60 °C; (e) PDC, MeOH (54% from **15**); (f) H_2, Pd/C, EtOH; (g) PhCOCl, (*N*,*N*-dimethylamino)pyridine, Et_3N (63% from **17**).

Anti Isomer of the Taxol Side Chain Methyl Ester. The intense development of many syntheses of taxol accounts for the special interest which was focused on the elaboration of its side chain showing both *syn* and *anti* diastereomerism.[12,13] In this connection, epoxy oxazolidine **7a** was transformed into the phenyl isoserine derivative **18** (Scheme 3), that is an *anti* stereoisomer of the taxol A-ring side chain.

The epoxide ring of compound **7a** was opened under the action of sodium azide, in the presence of ammonium chloride.[14] This stereospecific attack onto the oxirane moiety occurred in a totally regioselective manner and this special point will be addressed below. The masked aldehyde function was recovered by following the general procedure developed by Scolastico et al.,[15] who made use of thioacetal intermediates. To this end, the hydroxy group of compound **13** was protected as its *O*-benzyl analog; this reaction was followed by treatment of **14** by ethanedithiol with Lewis acid catalysis, and finally a methyl iodide-mediated hydrolysis of thioacetal **15** afforded aldehyde **16**. Product **16** was oxidized and yielded ester **17** which was hydrogenolyzed and treated with benzoyl chloride in order to produce the target molecule **18**. Its physical properties are the same as those reported for *ent*-**18**.[13c,16]

Chiral β-Amino Alcohol Used in the Construction of Peptide Isosteres. Several synthetic approaches to hydroxyethylamine isosteres have been reported because they are incorporated in many HIV-protease inhibitors.[17] In relation to such work, Dondoni et al.[18] have recently reported the synthesis of molecule **22** which is of special interest since its desilylated hydroxy derivative is a key intermediate in the preparation of Ro 31-8959, a potent and selective inhibitor of HIV proteinase.[19]

Scheme 4[a]



[a] Reaction conditions: (a) NaN_3, NH_4Cl, EtOH, reflux (97%); (b) H_2, $(Boc)_2O$, Pd/C, AcOEt (70%); (c) t-$BuMe_2SiOTf$, 2,6-lutidine, CH_2Cl_2, −78 °C (90%); (d) DIBAL-H, CH_2Cl_2, −78 °C; (e) SiO_2, CH_2Cl_2, H_2O, oxalic acid (55%).

Compound **22** was very easily obtained from epoxy oxazolidine *ent*-**7g** (Scheme 4) by using our methodology. The (2*S*,3*S*) absolute configuration of the target molecule **22** necessitated that, in this case, (*S*)-phenyl glycinol was used as the chiral starting material. Therefore, epoxy oxazolidine *ent*-**7g** was treated with sodium azide and, in this case as in the preceding one, a completely regioselective nucleophilic attack was observed (*vide infra*). Then, by a one-pot reaction,[20] the azido group of alcohol **19** was transformed into an *N*-Boc substituent yielding compound **20**. The hydroxy function of **20** was protected[21] as its *tert*-butyldimethylsilyloxy derivative. Finally, the oxazolidine moiety was removed in order to liberate the aldehyde function by using a modified procedure[11] which consists of reduction of the NCO_2Et group followed by mild acidic hydrolysis.[22] This final step afforded the protected β-amino alcohol **22**.

Theoretical Treatment of the Observed Regioselectivities. The cyclization involving a transient bromonium ion during the cyclocarbamation reaction (Scheme 1) as well as the substitution of epoxides **7a** and *ent*-**7g** (Schemes 3 and 4) are highly regioselective.[23] In both cases, nucleophilic attack occurs at the electrophilic

(12) Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 15−44.

(13) The isomerization of *anti* to *syn* side chain stereoisomer has been described: (a) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1723−1725. (b) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375−1376. (c) Gou, D. M.; Liu, Y. C.; Chen, C. S. *J. Org. Chem.* **1993**, *58*, 1287−1289. (d) Gennari, C.; Vulpetti, A.; Donghi, M.; Mongelli, N.; Vanotti, E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1723−1725.

(14) Commerçon, A.; Bezard, D.; Bernard, F.; Bourzat, J. D. *Tetrahedron Lett.* **1992**, *33*, 5185−5188.

(15) Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. *J. Org. Chem.* **1986**, *51*, 5041−5043.

(16) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387−6389.

(17) For some recent leading references, see: (a) Slee, D. H.; Laslo, K. L.; Elder, J. H.; Ollmann, I. R.; Gustchina, A.; Kervinen, J.; Zdanov, A.; Wlodawere, A.; Wong, C. H. *J. Am. Chem. Soc.* **1995**, *117*, 11867−11878. (b) Green, B. E.; Chen, X.; Norbeck, D. W.; Kempf, D. J. *Synlett* **1995**, 613−614. (c) Beaulieu, P. L.; Wernic, D.; Duceppe, J. S. ; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317−3320. (d) Keenan, R. M.; Eppley, D. F.; Tomaszek, T. A., Jr. *Tetrahedron Lett.* **1995**, *36*, 819−822.

(18) Dondoni, A.; Perrone, D.; Merino, P. *J. Org. Chem.* **1995**, *60*, 8074−8080.

(19) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656−3664.

(20) Saito, S.; Nakajima, H.; Inaba, M.; Moriwake, T. *Tetrahedron Lett.* **1989**, *30*, 837−838.

(21) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455−3458.

(22) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63−65.

(23) Nucleophilic attacks of oxazolidines **5c** and **5f** by organo cuprates, eventually leading to pheromones, have been described. They show the same regioselectivity pattern as in the cases reported here. See: Agami, C.; Couty, F.; Venier, O. *Synlett* **1996**, 511−512.

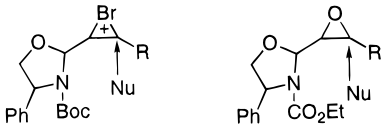
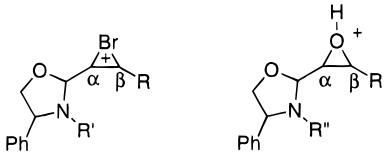


Figure 1. Regioselectivity of nucleophilic attacks.

Scheme 5



23a-b **24a-b**

	R	R'	R"
23a	Pr	Boc	-
23b	Ph	Boc	-
24a	Pr		COOEt
24b	Ph		COOEt

center which is the more distant one from the oxazolidine ring (see Figure 1).

Clearly the intramolecular nature of the bromocarbamation reaction should be considered. As mentioned above, the 6-*endo*-*tet* ring closure appeared to be preferred over the corresponding 5-*exo*-*tet* process. Although neither process can be favored on the sole basis of Baldwin's rules,[24] it has been frequently observed that intramolecular attack onto epoxides generally follows the 5-*exo* path unless there is some kind of positive charge stabilization favoring the 6-*endo* process.[25] On the other hand, intermolecular nucleophilic attacks onto epoxides linked to heterocycles (acetals,[26,4] furanosides,[4] imidazolidines,[27] or oxazolidines[28]) were reported to occur, as in the present cases, on the distal oxiranyl carbon atom.

It was therefore appealing to assume that the above-reported regioselectivities may proceed from the same cause. Thus, we have undertaken an AM1 series of calculations on bromonium ions **23a**,**b** and on protonated epoxides[29] **24a**,**b** Table 2.

These calculations unambiguously indicate that in each case (i) the fraction of positive charge is much larger in the Cβ position, that is on the carbon atom which is the more distant one from the heterocycle, in agreement with the experimental results; (ii) the bond indices are consistent with the positive charge disposal since the Cβ−O bond of protonated epoxides or the Cβ−Br bond in bromonium ions show the smaller bond index. The larger value of positive charge on the Cβ center is obviously due to the electroattracting effect of the C−O and C−N bonds belonging to the oxazolidine moiety. Analogous calculations were performed on the N-unsubstituted compounds **23a** and **24a** (R′ = R″ = H, R = Pr), that is on molecules in which the C−N oxazolidine bond has a less electro-

(24) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734−738.
(25) See ref 2, pp 732−733.
(26) Fourneau, J. P.; Chantalou, S. *Bull. Soc. Chim. Fr.* **1945**, 845−864.
(27) Behrens, C. H.; Sharpless, K. B. *Aldrichim. Acta* **1983**, *16*, 67−79.
(28) Bernardi, A.; Cardani, S.; Scolastico, C.; Villa, R. *Tetrahedron* **1990**, *46*, 1987−1998.
(29) The substitution of epoxides **7a** and *ent*-**7g** by azide ion was performed in the presence of ammonium chloride.

Table 2. AM1 Calculations

	charges		bond indices	
compound	Cα	Cβ	Cα-X	Cβ-X
23a	−0.15	+0.16	0.815	0.481
23b	−0.25	+0.10	0.922	0.006
24a	+0.07	+0.20	0.828	0.607
24b	−0.02	+0.09	1.015	0.006

attracting effect. This second series of calculations reveals that the positive charge on the Cβ center is less pronounced in such cases: +0.13 and +0.06, respectively. It can therefore be concluded that the above reported regioselectivities are, at least partially, directed by the distribution of the positive charge at the electrophilic centers.

In conclusion, the reported regio- and stereoselective cleavage of the epoxide moiety eventually affords functionalized aldehydes. The synthesis of enantiopure α-hydroxy β-amino aldehydes or esters has received considerable attention,[13] and this new methodology offers an alternative access to these biologically interesting compounds.

Experimental Section

General Methods. ^{1}H NMR spectra ($CDCl_3$ solutions unless otherwise stated) were carried out at 250 or 400 MHz, and ^{13}C NMR spectra ($CDCl_3$ solutions unless otherwise stated) were carried out at 62.9 or 100 MHz. Melting points are uncorrected. Column chromatography was performed on silica gel 230−400 mesh with various mixture of diethyl ether (E) and petroleum ether (PE). Tetrahydrofuran (THF) and dichloromethane were freshly distilled before use, respectively, from benzophenone ketyl and from CaH_2.

General Procedure for the Synthesis of Alkenyl Oxazolidine 5a−f. Unsaturated aldehydes **4a−f** (15 mmol) were reacted with (*R*)-phenylglycinol (2 g, 14.6 mmol) in dry CH_2Cl_2 (30 mL) in the presence of 4 Å molecular sieves (10 g). The mixture was kept at ambient temperature for 3 h, filtered, and concentrated. The resulting residue was dissolved in EtOAc (60 mL), treated with di-*tert*-butyl dicarbonate (3.3 g, 15 mmol), refluxed for 15 h, and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE 10/90) gave pure oxazolidines **5a−f**.

(2*R*,4*R*,2′*E*)-4-Phenyl-2-(2-phenylvinyl)oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5a): yield 93%; yellow solid, mp 72 °C. ^{1}H NMR: 1.3−1.5 (bm, 9H), 4.02 (dd, J = 5.3 and 8.8 Hz, 1H), 4.3 (dd, J = 7 and 8.8 Hz, 1H), 4.9 (bs, 1H), 5.75 (bs, 1H), 6.25 (dd, J = 5 and 15.6 Hz, 1H), 6.75 (d, J = 15.6 Hz, 1H), 7.1−7.5 (m, 10H); ^{13}C NMR: 28.7, 61, 73.8, 81, 90.5, 126.7, 126.9, 127.3, 127.9, 128.6, 129, 134.4, 136.6, 141, 154; IR ($CHCl_3$): 1705, 1160 cm^{-1}. $[\alpha]_{20}^{D}$: +8 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.03; H, 7.25; N, 4.07.

(2*R*,4*R*,2′*E*)-2-(1-Methyl-2-phenylvinyl)-4-phenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5b): yield 62%; white solid, mp 101 °C. ^{1}H NMR: 1.4 (bs, 9H), 1.94 (s, 3H), 4.12 (dd, J = 5.2 and 8.7 Hz, 1H), 4.29 (dd, J = 7.1 and 8.9 Hz, 1H), 4.96 (t, J = 6.2 Hz, 1H), 5.6 (s, 1H), 6.67 (s, 1H), 7.2−7.4 (m, 10H); ^{13}C NMR: 13.6, 28.3, 60.8, 72.6, 80.7, 94.2, 126.8, 127.3, 128.2, 129.1, 135, 137.2, 140.5, 154.4. $[\alpha]_{20}^{D}$: +8 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.59; H, 7.49; N, 3.76.

(2*R*,4*R*,2′*E*)-4-Phenyl-2-propenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5c): yield 57%; oil. ^{1}H NMR: 1.3 (bs, 9H), 1.73 (dd, J = 1.5 and 6.6 Hz, 3H), 3.92 (dd, J = 5 and 8.8 Hz, 1H), 4.18 (dd, J = 6.7 and 8.8 Hz, 1H), 4.85 (bm, 1H), 5.5−5.63 (m, 2H), 5.89 (m, 1H), 7.1−7.35 (m, 5H); ^{13}C NMR: 17.6, 28.3, 60.5, 73, 80.3, 90.1, 126.5, 127.3, 128.4, 128.6, 130.8, 140.9, 153.4. $[\alpha]_{20}^{D}$: −62 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.58; H, 8.08; N, 4.95.

(2*R*,4*R*,2′*E*)-2-(1-Methylbut-1-enyl)-4-phenyl-2-propenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5d): yield 80%; oil. ^{1}H NMR: 0.93 (t, J = 7.5 Hz, 3H), 1.3 (bs, 9H), 1.55 (s, 3H), 2.05 (q, J = 7.4 Hz, 2H), 4.02 (dd, J = 4.8 and 8.8, 1H), 4.18 (dd, J = 7 and 8.8 Hz, 1H), 4.87 (bt J = 5 Hz, 1H), 5.38 (bs, 1H), 5.6 (bt, J = 7 Hz, 1H), 7.1−7.5 (m, 5H); ^{13}C NMR: 11.4, 13.8, 21, 28.2, 60.7, 72.3, 80.3, 94.1, 127.2, 127.3, 128.3, 131.5, 140.8, 154.3; IR ($CHCl_3$): 1690, 990 cm^{-1}. $[\alpha]_{20}^{D}$: −47 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.72; H, 8.69; N, 4.48.

(2*R*,4*R*,2′*E*,4′*E*)-2-Penta-1,3-dienyl-4-phenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5e): yield 80%; oil. ^{1}H NMR: 1.37 (bs, 9H), 1.8 (d, J = 6.6 Hz, 3H), 4.0 (dd, J = 5.3 and 8.8 Hz, 1H), 4.3 (dd, J = 7.6 and 7.6 Hz, 1H), 4.95 (bs, 1H), 5.66 (bs, 2H), 5.83 (m, 2H), 6.14 (ddd, J = 1.4, 10.7 and 13.6 Hz, 1H), 6.4 (bm, 1H), 7.2−7.4 (m, 5H); ^{13}C NMR: 13.8, 28.7, 60.9, 73.6, 80.8, 90.4, 126.9, 127.2, 127.8, 128.9, 130.8, 132.1, 134.6, 141.2, 153.8; IR ($CHCl_3$): 1690, 905 cm^{-1}. $[\alpha]_{20}^{D}$: −57.3 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_3$: C, 72.35; H, 7.99; N, 4.44. Found: C, 72.34; H, 8.08; N, 4.46.

(2*R*,4*R*,2′*E*)-2-Pent-1-enyl-4-phenyloxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5f): yield 81%; oil. ^{1}H NMR: 0.95 (t, J = 7.4 Hz, 3H), 1.38 (s, 9H), 1.47 (sext, J = 7.4 Hz, 2H), 2.12 (q, J = 7.1 Hz, 1H), 4.01 (dd, J = 5 and 8.7 Hz, 1H), 4.28 (dd, J = 7 and 8.6 Hz, 1H), 5.62 (bm, 2H), 5.96 (bdd, 7.1 and 14.8 Hz, 1H), 7.3−7.4 (m, 5H); ^{13}C NMR: 13.6, 22, 28.2, 34.1, 60.5, 72.8, 80.3, 90.1, 126.5, 127.3, 128.4, 135.8, 140.9, 153.4; IR ($CHCl_3$): 1700 cm^{-1}. $[\alpha]_{20}^{D}$: −57.3 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.8; H, 8.75; N, 4.39.

(2*S*,4*S*,2′*E*)-4-Phenyl-2-(3-phenylpropenyl)oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (*ent*-5g). 4-Phenyl-2-butenal[30] (**4g**) (2 g, 15 mmol) was reacted with (*S*)-phenylglycinol (2 g, 14.6 mmol) in dry CH_2Cl_2 (50 mL) in the presence of 4 Å molecular sieves (15 g). The mixture was kept at ambient temperature for 0.5 h, filtered, and concentrated. The resulting residue was dissolved in EtOAc (60 mL), treated with di-*tert*-butyl dicarbonate (6.5 g, 30 mmol), stirred at rt for 18 h, and concentrated in vacuo. Purification of the residue by flash chromatography using E/PE (10/90) afforded *ent*-**5g** (3.2 g, 60%) as a white solid: mp 58 °C. ^{1}H NMR: 1.27 (bs, 9H), 3.42 (d, J = 6.8 Hz, 2H), 3.94 (d, J = 5.2 and 8.7 Hz, 1H), 4.25 (dd, J = 6.8 and 8.7 Hz, 1H), 4.9 (bs, 1H), 5.58 (bs, 1H), 5.64 (bm, 1H), 6.04 (bm, 1H), 7.1−7.3 (m, 10H); ^{13}C NMR: 28.3, 38.5, 60.6, 73.3, 80.5, 89.8, 126.3, 126.6, 127.4, 128.5, 128.7, 134.1, 139.7, 140.8, 153.5; IR ($CHCl_3$): 1685 cm^{-1}. $[\alpha]_{20}^{D}$: −16.4 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{23}H_{27}NO_3$: C, 75.59; H, 7.45; N, 3.83. Found: C, 75.47; H, 7.52; N, 3.77.

General Procedure for the Synthesis of Bicyclic Compounds 6a−g. NBS (0.57 g, 3.5 mmol) was added to a solution of oxazolidine **5** (3.2 mmol) in DME/H_2O (10 mL/10 mL), and the mixture was stirred at rt for 3 h. Water was then added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography using a variable E/PE mixture or by crystallization gave pure bicyclic compounds **6a−f** and *ent*-**6g**.

(3*R*,7*S*,8*S*,9*R*)-8-Bromo-3,7-diphenyltetrahydrooxazolo-[3,2-*c*][1,3]oxazin-5-one 6a: crystallized from absolute EtOH; yield 80%; colorless crystals: mp 178 °C. ^{1}H NMR: 4.05 (dd, J = 8.8 and 10.8 Hz, 1H), 4.15 (dd, J = 9 and 1.4 Hz, 1H), 4.25 (dd, J = 6.5 and 9 Hz, 1H), 4.94 (dd, J = 1.4 and 6.5 Hz, 1H), 5.13 (d, J = 8.8 Hz, 1H), 5.2 (d, J = 10.8 Hz, 1H), 7.15−7.35 (m, 10H); ^{13}C NMR: 47.1, 60.9, 74.0, 81.3, 89.3, 126.7, 127.8, 128.4, 128.7, 128.9, 129.8, 134.8, 139.8, 148.6; IR ($CHCl_3$): 1715 cm^{-1}. $[\alpha]_{20}^{D}$: +104 (*c* 1.3 $CHCl_3$). Anal. Calcd for $C_{18}H_{16}NO_3Br$: C, 57.77; H, 4.31; N, 3.74. Found: C, 57.75; H, 4.32; N, 3.74.

(3*R*,7*S*,8*S*,9*R*)-8-Bromo-8-methyl-3,7-diphenyltetrahydrooxazolo[3,2-*c*] [1,3]oxazin-5-one (6b): chromatographed (E/PE: 50/50); yield 90%; colorless crystals: mp 172 °C. ^{1}H NMR: 1.72 (s, 3H), 4.4 (m, 2H), 4.98 (m, 1H), 5.43 (s, 1H), 5.53 (s, 1H), 7.3−7.5 (m, 10H); ^{13}C NMR: 16.7, 57.9, 60.1, 73.9, 83.4, 92.6, 127.7, 127.73, 127.9, 128.4, 128.7, 129, 129.3, 132.2, 139, 148.6. $[\alpha]_{20}^{D}$: +197 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{19}H_{18}NO_3Br$: C, 58.78; H, 4.67; N, 3.61. Found: C, 58.80; H, 4.64; N, 3.54.

(3*R*,7*S*,8*S*,9*R*)-8-Bromo-7-methyl-3-phenyltetrahydrooxazolo[3,2-*c*][1,3] oxazin-5-one (6c): crystallized from absolute EtOH; 53% overall yield from aldehyde **4c**; colorless crystals: mp 169 °C. ^{1}H NMR: 1.52 (d, J = 6.2 Hz, 3H), 3.75 (dd, J = 8.8 and 10.7 Hz, 1H), 4.06 (dd, J = 1.3 and 9.2 Hz, 1H), 4.18 (dd, J = 6.5 and 9.2 Hz, 1H), 4.39 (dq, J = 6.2 and 10.7 Hz, 1H), 4.85 (dd, J = 1.3 and 6.5 Hz, 1H), 4.95 (d, J = 8.8 Hz, 1H), 7.15−7.3 (m, 5H); ^{13}C NMR: 28.6, 47, 60.6, 73.8, 75.6, 89, 126.5, 128.1, 128.7, 139.8, 148.6. $[\alpha]_{20}^{D}$: +112 (*c* 0.7 $CHCl_3$). Anal. Calcd for $C_{13}H_{14}NO_3Br$: C, 50.02; H, 4.52; N, 4.49. Found: C, 50.00; H, 4.42; N, 4.45.

(3*R*,7*S*,8*S*,9*R*)-8-Bromo-7-ethyl-8-methyl-3-phenyltetrahydrooxazolo[3,2-*c*][1,3]oxazin-5-one (6d): chromatographed (E/PE: 50/50); yield 73%; colorless crystals: mp 141 °C. ^{1}H NMR: 1.05 (t, J = 7.3 Hz, 3H), 1.49 (d, J = 0.8 Hz, 3H), 1.5−1.7 (m, 1H), 2.0−2.2 (m, 1H), 4.18 (d, J = 10.2 Hz, 1H), 4.24 (m, 2H), 4.81 (t, J = 4.4 Hz, 1H), 5.11 (d, J = 0.6 Hz, 1H), 7.15−7.5 (m, 5H); ^{13}C NMR: 10.9, 16.6, 22.1, 57.9, 59.9, 73.7, 83.6, 92.3, 127.6, 128.2, 128.5, 139.1, 148.9; IR ($CHCl_3$): 1715 cm^{-1}. $[\alpha]_{20}^{D}$: +24 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{15}H_{18}NO_3Br$: C, 52.96; H, 5.33; N, 4.12. Found: C, 53.30; H, 5.26; N, 4.14.

(3*R*,7*S*,8*S*,9*R*,*E*)-8-Bromo-3-phenyl-7-propenyltetrahydrooxazolo[3,2-*c*][1,3]oxazin-5-one (6e): crystallized from absolute EtOH; yield 80%; colorless crystals: mp 113 °C. ^{1}H NMR: 1.7 (dd, J = 0.7 and 6.5 Hz, 3H), 3.79 (dd, J = 8.9 and 10.7 Hz, 1H), 4.1 (d, J = 9.1 Hz, 1H), 4.2 (dd, J = 7.1 and 9.2 Hz, 1H), 4.64 (dd, J = 7.7 and 10.7 Hz, 1H), 4.88 (d, J = 6.3 Hz, 1H), 4.98 (d, J = 8.8 Hz, 1H), 5.44 (ddd, J = 1.5, 7.7 and 15 Hz, 1H), 5.9 (m, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR: 13.6, 45.8, 60.4, 73.3, 79.7, 90.6, 124.5, 126.4, 127.8, 128.4, 134.5, 139.8, 148.3; IR ($CHCl_3$): 1720 cm^{-1}. $[\alpha]_{20}^{D}$: +68 (*c* 0.8 $CHCl_3$). Anal. Calcd for $C_{15}H_{16}NO_3Br$: C, 53.27; H, 4.77; N, 4.14. Found: C, 53.37; H, 4.84; N, 4.31.

(3*R*,7*S*,8*S*,9*R*)-8-Bromo-3-phenyl-7-propyltetrahydrooxazolo[3,2-*c*][1,3] oxazin-5-one (6f): crystallized from absolute EtOH; 77% overall yield from aldehyde **4f**; colorless crystals: mp 126 °C. ^{1}H NMR: 0.97 (t, J = 7.4 Hz, 3H), 1.4−1.5 (m, 1H), 1.55−1.7 (m, 1H), 1.7−1.82 (m, 1H), 2.02−2.15 (m, 1H), 3.9 (dd, J = 8.7 and 10.7 Hz, 1H), 4.19 (dd, J = 1.1 and 9.4 Hz, 1H), 4.3 (dd, J = 6.6 and 9.3 Hz, 1H), 4.38 (m, 1H), 4.98 (dd, J = 1 and 6.5 Hz, 1H), 5.05 (d, J = 8.7, 1H), 7.3−7.4 (m, 5H); ^{13}C NMR: 13.5, 17.4, 34.1, 45.6, 60.7, 73.8, 89.1, 126.5, 128.1, 128.7, 139.9, 149.1; IR ($CHCl_3$): 1715 cm^{-1}. $[\alpha]_{20}^{D}$: +49 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{15}H_{18}NO_3Br$: C, 52.96; H, 5.33; N, 4.12. Found: C, 52.95; H, 5.42; N, 4.11.

(3*S*,7*R*,8*R*,9*S*)-7-Benzyl-8-bromo-3-phenyltetrahydrooxazolo[3,2-*c*][1,3]oxazin-5-one (*ent* 6g): crystallized from *i*-PrOH; yield 92%; colorless crystals: mp 196 °C. ^{1}H NMR: 3.1 (dd, J = 4.8 and 14.7 Hz, 1H), 3.37 (dd, J = 3.1 and 14.7 Hz, 1H), 3.65 (dd, J = 8.8 and 10.7 Hz, 1H), 3.97 (d, J = 9.1 Hz, 1H), 4.18 (dd, J = 6.6 and 9.1 Hz, 1H), 4.65 (ddd, J = 3.1, 4.8 and 10.7 Hz, 1H), 4.85 (d, J = 6.2 Hz, 1H), 5.01 (d, J = 8.8 Hz, 1H), 6.87 (dd, J = 1.6 and 7.2 Hz, 2H), 7.1−7.4 (m, 8H); ^{13}C NMR: 37, 44.3, 60.5, 73.9, 74, 88.5, 126, 127.4, 128, 128.69, 128.73, 130.2, 134.3, 139.5, 148.5; IR ($CHCl_3$): 1710 cm^{-1}. $[\alpha]_{20}^{D}$: −13 (*c* 1 $CHCl_3$). Anal. Calcd for $C_{19}H_{18}NO_3Br$: C, 58.78; H, 4.67; N, 3.61. Found: C, 58.88; H, 4.78; N, 3.53.

General Procedure for the Synthesis of Epoxides 7a−f and *ent*-7g. Bicyclic compounds **6a−f** and *ent*-**6g** (1 mmol) were added to a solution of NaOEt (5 mmol) in absolute EtOH (8 mL), and the mixture was stirred at rt for 3 h. Saturated aqueous ammonium chloride was then added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography using an E/PE eluent gave pure epoxides **7a−f** and *ent*-**7g**.

(2R,4*R*,2′*R*,3′*S*)-4-Phenyl-2-(3-phenyloxiran-2-yl)oxazolidine-3-carboxylic Acid Ethyl Ester (7a): E/PE: 60/40; 72% overall yield from aldehyde **4a**; white solid, mp 83 °C. ^{1}H NMR: 1−1.35 (bm, 3H), 3.38 (bs, 1H), 3.85 (d, J = 1.9 Hz, 1H), 4−4.2 (m, 2H), 4.14 (dd, J = 6.9 and 8.3 Hz, 1H), 4.33

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(dd, J = 6.7 and 8.8 Hz, 1H), 4.94 (t, J = 6.6 Hz, 1H), 5.58 (bs, 1H), 7.1−7.45 (m, 10H); ^{13}C NMR: 14.5, 55.1, 60.9, 62, 62.6, 74.2, 88, 125.8, 126.8, 127.8, 128.4, 128.6, 128.65, 136.4, 139.4, 155; IR ($CHCl_3$): 1670, 1250 cm^{-1}; $[\alpha]_{20}^{D}$: +17 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.79; H, 6.22; N, 4.26.

(2*R*,4*R*,2′*R*,3′*S*)-2-(2-Methyl-3-phenyloxiran-2-yl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (7b): E/PE: 40/60; yield 85%; white solid, mp 65 °C. ^{1}H NMR: 1.05−1.2 (bs, 6H), 4−4.15 (bs, 3H), 4.19 (t, J = 8.7 Hz, 1H), 4.30 (t, J = 8.6 Hz, 1H), 4.88 (bt, J = 8 Hz, 1H), 5.45 (bs, 1H), 7.17−7.3 (m, 8H), 7.4−7.5 (m, 2H); ^{13}C NMR: 13.6, 14.6, 59.9, 62.1, 62.2, 64, 74.2, 92.1, 126.7, 127.5, 127.8, 127.9, 128.2, 128.6, 135.4, 138.9, 156. $[\alpha]_{20}^{D}$: +24 (*c* 0.5 $CHCl_3$).

(2*R*,4*R*,2′*R*,3′*S*)-2-(3-Methyloxiran-2-yl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (7c): E/PE: 30/70; yield 80%; oil. ^{1}H NMR: 0.9−1.2 (bm, 3H), 1.27 (d, J = 5.1 Hz, 3H), 2.98 (m, 2H), 4.01 (dd, J = 6.8 and 8.6 Hz, 1H), 3.9−4.15 (bm, 2H), 4.23 (dd, J = 7 and 8.7 Hz, 1H), 4.86 (m, 1H), 5.43 (m, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR: 14.4, 17.0, 51.2, 59.5, 60.8, 61.8, 74.0, 88.3, 126.7, 127.7, 128.5, 139.5, 155.0. $[\alpha]_{20}^{D}$: +16 (*c* 1.8 $CHCl_3$). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.92; H, 6.96; N, 5.04.

(2*R*,4*R*,2′*R*,3′*S*)-2-(2-Methyl-3-ethyloxiran-2-yl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (7d): E/PE: 20/80; yield 71%; oil. ^{1}H NMR: 1.03 (t, J = 8.4 Hz, 3H), 1.16 (bs, 3H), 1.43 (s, 3H), 1.55 (m, 1H), 1.7 (m, 1H), 2.95 (t, J = 6.5 Hz, 1H), 4.1 (m, 2H), 4.18 (t, J = 8.6 Hz, 1H), 4.31 (dd, J = 7.5 and 8.5 Hz, 1H), 4.87 (bt, J = 7.8 Hz, 1H), 5.4 (bs, 1H), 7.2−7.6 (m, 5H); ^{13}C NMR: 10.3, 14, 14.4, 21.25, 60.2, 61.3, 61.8, 61.9, 73.9, 92, 127.4, 127.7, 128.4, 139, 154.1; IR ($CHCl_3$): 1690 cm^{-1}. $[\alpha]_{20}^{D}$: +2.2 (*c* 0.5 $CHCl_3$).

(2*R*,4*R*,2′*R*,3′*S*,4*E*)-4-Phenyl-2-(3-propenyl-3-oxiran-2-yl)oxazolidine-3-carboxylic Acid Ethyl Ester (7e): E/PE: 20/80; yield 80%; oil. ^{1}H NMR: 1.11 (bs, 3H), 1.7 (dd, J = 1.6 and 66Hz, 3H), 3.22 (bs, 1H), 3.33 (dd, J = 2.1 and 8.3 Hz, 1H), 4.05 (m, 3H), 4.25 (dd, J = 7 and 8.8 Hz, 1H), 4.86 (t, J = 6.6 Hz 1H), 5.18 (ddd, J = 1.6, 8.3 and 15.4 Hz, 1H), 5.46 (bs, 1H), 5.9 (m, 1H), 7.15−7.5 (m, 5H); ^{13}C NMR: 14.4, 17.9, 50.8, 59.9, 60.8, 61.8, 74, 88.1, 126.7, 127.3, 127.7, 128.5, 132.7, 139.4, 154.9; IR ($CHCl_3$): 1690 cm^{-1}; $[\alpha]_{20}^{D}$: +15 (*c* 0.5 $CHCl_3$).

(2*R*,4*R*,2′*R*,3′*S*)-4-Phenyl-2-(3-propyl-3-oxiran-2-yl)-oxazolidine-3-carboxylic Acid Ethyl Ester (7f): E/PE: 30/70; 68% overall yield from aldehyde **4f**; oil. ^{1}H NMR: 0.85 (t, J = 7.2 Hz, 3H), 0.9−1.2 (bm, 3H), 1.3−1.6 (m, 4H), 2.87 (m, 1H), 2.99 (m, 1H), 3.8−4.1 (m, 3H), 4.16 (dd, J = 7.2 and 8.7 Hz, 1H), 4.8 (m, 1H), 5.38 (m, 1H), 7.1−7.4 (m, 5H); ^{13}C NMR: 13.5, 14.1, 19.0, 33.0, 54.6, 58.1, 60.5, 61.3, 73.5, 88.1, 126.4, 127.3, 128.1, 139.3, 154.5; IR ($CHCl_3$): 1690, 1250 cm^{-1}. $[\alpha]_{20}^{D}$: −13 (*c* 0.3 $CHCl_3$). Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.86; H, 7.63; N, 4.66.

(2*S*,4*s*,2′*s*,3′*r*)-2-(3-Benzyl-3-oxiran-2-yl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (*ent*-7g): E/PE: 40/60; yield 97%; oil. ^{1}H NMR: 1.07 (t, J = 7 Hz, 3H), 2.82 (dd, J = 5.1 and 14.4 Hz, 1H), 2.97 (dd, J = 5.4 and 14.4 Hz, 1H), 3.17 (bs, 1H), 3.22 (dt, J = 2 and 5.5 Hz, 1H), 4.00 (dd, J = 7.3 and 8 Hz, 1H), 4.02 (q, J = 7 Hz, 1H), 4.24 (dd, J = 6.9 and 8.8 Hz, 1H), 4.86 (bt, J = 5.1 Hz, 1H), 5.45 (bs, 1H), 7.15−7.3 (m, 10H); ^{13}C NMR: 14.3, 37.7, 55.2, 58.3, 60.8, 61.8, 73.9, 88.2, 126.7, 127.7, 128.5, 128.6, 129, 136.8, 139.2, 154.9. IR ($CHCl_3$): 1715 cm^{-1}; $[\alpha]_{20}^{D}$: −4 (*c* 0.7 $CHCl_3$). Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.23; H, 6.57; N, 3.96.

Bromocarbamation of Compound 5a with Bromine. A 1 M solution of bromine in CH_2Cl_2 (3.1 mL) was added to a solution of oxazolidine **5a** (1 g, 2.8 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at 0 °C for 1 h. A saturated aqueous solution of $NaHCO_3$ was then added, and the resulting mixture was decolorized with a few drops of 0.1 N solution of $Na_2S_2O_3$. After extraction with CH_2Cl_2, the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The **8**/**9** (X = Br) ratio was determined by comparing the corresponding ^{1}H NMR signals in the crude resulting mixture. A sample of compound **9** (X = Br) was isolated from compound **8** (which corresponds to the above-described compound **6a**) by flash chromatography using a (40/60) E/PE mixture. White solid: mp 232 °C. ^{1}H NMR: 3.87 (dd, J = 7.6 and 9.1 Hz, 1H), 3.98 (dd, J = 8 and 11.1 Hz, 1H), 4.54 (dd, J = 7.7 and 9.1 Hz, 1H), 5.13 (d, J = 11 Hz), 5.2−5.3 (m, 1H), 5.3 (d, J = 7.9 Hz, 1H), 7.2−7.4 (m, 10H); ^{13}C NMR: 46.2, 61.3, 72.8, 79.5, 91.3, 126.3, 127.9, 128.3, 128.7, 129.0, 129.9, 134.3, 138.1, 151.3. $[\alpha]_{20}^{D}$: −40 (*c* 0.15 $CHCl_3$).

(2*R*,4*R*,1′*R*,2′*r*)-2-(2-Azido-1-hydroxy-2-phenylethyl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (13). Sodium azide (13.4 g, 206 mmol) and water (70 mL) were successively added to a solution of epoxy oxazolidine **7a** (7 g, 20.6 mmol) and ammonium chloride (10.9 g, 206 mmol) in EtOH (380 mL). The mixture was refluxed for 24 h and concentrated. Water was then added, and the resulting mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$). After evaporation, azido alcohol **13** was isolated as an oil (7 g), and the crude product was used as such in the next step. A sample was purified by flash chromatography (E/PE: 60/40). ^{1}H NMR: 1.0 (t, J = 7.1 Hz, 3H), 3.96−4.08 (m, 3H), 4.11 (dd, J = 6.7 and 8.9 Hz, 1H), 4.18 (dd, J = 6.9 and 8.8 Hz, 1H), 4.72 (d, J = 3.5 Hz, 1H), 4.85−4.9 (d, J = 8.3 Hz, 1H), 4.95 (dd, J = 6.7 and 6.9 Hz, 1H), 7.1−7.55 (m, 10H); ^{13}C NMR: 14.2, 60.5, 62.4, 66.4, 73.6, 76.1, 90.2, 126.2, 127.8, 128.5, 128.7, 134.9, 139.4, 156.7. $[\alpha]_{20}^{D}$: −47 (*c* 0.7 $CHCl_3$).

(2*R*,4*R*,1′*R*,2′*r*)-2-[2-Azido-1-(benzyloxy)-2-phenylethyl]-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (14). Sodium hydride (0.625 g, 60% dispersion in mineral oil, 16.3 mmol) was added to a solution of compound **13** (7 g, 20.6 mmol) in DMF (80 mL) at 0 °C. The mixture was stirred for 15 min, and then benzyl bromide (1.93 mL, 16.3 mmol) was added. The mixture was stirred for 15 min and then hydrolyzed with an ammonium chloride saturated aqueous solution. The resulting mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE: 20/80) gave compound **14** (4.4 g, 71% overall yield from **7a**) as a yellow solid: mp 70 °C. ^{1}H NMR: 1.03 (t, J = 7.1 Hz, 3H), 3.65 (dd, J = 4.1 and 7.2 Hz, 1H), 3.96−4.1 (m, 4H), 4.2 (m, 1H), 4.7 (d, J = 7.3 Hz, 1H), 4.95 (m, 1H), 5.5 (m, 1H), 6.7−7.5 (m, 15H); ^{13}C NMR: 14.4, 61.4, 62.1, 66.0, 73.2, 75.1, 83.6, 90.4, 126.9, 127.5, 127.6, 128.1, 128.4, 128.6, 128.9, 136.6, 139.5, 156.3. IR ($CHCl_3$): 2100, 1670 cm^{-1}. $[\alpha]_{20}^{D}$: −59 (*c* 0.6 $CHCl_3$).

(1*R*,2*r*)-2-(Benzyloxy)-2-[1,3]dithiolan-2-yl-1-phenylethyl Azide (15). Boron trifluoride etherate (0.52 mL, 4.2 mmol) was added to a solution of oxazolidine **14** (1 g, 2.1 mmol) and ethanedithiol (1.23 mL, 14.7 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 3 days and then hydrolyzed by an aqueous saturated solution with sodium hydrogen carbonate. The resulting mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE: 5/95) gave compound **15** (0.53 g, 73%) as a solid: mp 57 °C. ^{1}H NMR: 3−3.3 (m, 4H), 3.6 (t, J = 6.1 Hz, 1H), 4.3−4.65 (m, 2H), 4.51 (d, J = 6.2 Hz, 1H), 4.72 (d, J = 6.1 Hz, 1H),7.1−7.5 (m, 10H); ^{13}C NMR: 38.2, 38.9, 54.6, 68.0, 76.3, 86.1, 127.6, 128.1, 128.5, 128.6, 128.7, 135.6, 137.5. IR ($CHCl_3$): 2110 cm^{-1}. $[\alpha]_{20}^{D}$: −66 (*c* 1.7 $CHCl_3$).

(1*R*,2*r*)-3-Azido-2-(benzyloxy)-3-phenylpropionaldehyde (16). Methyl iodide (3.6 mL, 58 mmol) and water (3.2 mL) were successively added to a solution of thioacetal **15** (1 g, 2.9 mmol) and calcium carbonate (0.87 g, 8.7 mmol) in acetone (12.8 mL). The mixture was heated at 60 °C for 4 days and concentrated. Water was then added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$). After evaporation, aldehyde **16** was isolated as a colorless oil (0.75 g, 90%), and the crude product was used as such in the next step. ^{1}H NMR: 4.01 (dd, J = 2 and 5.8 Hz, 1H), 4.56−4.7 (m, 2H), 4.6 (d, J = 5.8 Hz, 1H), 7.1−7.7 (m, 10H), 9.6 (d, J = 2 Hz, 1H); ^{13}C NMR: 65.6, 73.6, 84.8, 128.1, 128.4, 128.7, 128.9, 134.8, 136.6, 200.4.

(1*R*,2*r*)-3-Azido-2-(benzyloxy)-3-phenylpropionic Acid Methyl Ester (17). PDC (4 g, 11.2 mmol) was added to a solution of aldehyde **16** (0.63 g, 2.24 mmol) in DMF/MeOH (11 mL/1.1 mL), and the mixture was stirred at rt for 19 h. Water

and ether were then added, and the resulting mixture was filtered on Celite. The filtrate was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE: 5/95) gave compound **17** (0.38 g, 60%) as an oil. ^{1}H NMR: 3.69 (s, 3H), 4.07 (d, J = 7.3 Hz, 1H), 4.3−4.6 (m, 2H), 4.75 (d, J = 7.3 Hz, 1H), 7.-7.4 (m, 10H); ^{13}C NMR: 52.3; 66.0; 73.0; 80.6; 128.0; 128.1; 128.6; 128.9; 135.4; 136.5; 170.4. IR ($CHCl_3$): 2115, 1740 cm^{-1}. $[\alpha]_{20}^{D}$: −41 (*c* 1 $CHCl_3$).

(1*R*,2*r*)-3-(Benzoylamino)-2-(benzyloxy)-3-phenylpropionic Acid Methyl Ester (18). A mixture of ester **17** (0.067 g, 0.24 mmol) and 5% Pd on carbon (0.04 g) in methanol (5 mL) was refluxed under hydrogen (1 atm) for 36 h. The catalyst was filtred on Celite, and the filtrate was evaporated. The resulting solid (0.04 g) and triethylamine (0.01 g, 0.1 mmol) were dissolved in CH_2Cl_2 (1 mL), and (dimethylamino)-pyridine (0.002 g, 0.002 mmol) and benzoyl chloride (0.024 mL, 0.2 mmol) were successively added. The mixture was stirred at rt for 1.5 h. Water was then added, and the resulting mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE: 75/25) gave compound **18** (0.044 g, 63%) as a solid: mp 156−157 °C. ^{1}H NMR: 2.97 (d, J = 6.6 Hz, 3H), 3.67 (s, 3H), 4.65 (dd, J = 3.5 and 6.6 Hz, 1H), 5.56 (dd, J = 3.5 and 6.6 Hz, 1H), 7.09 (d, J = 9 Hz, 1H), 7.2−7.5 (m, 8H), 7.7−7.8 (m, 2H); ^{13}C NMR: 52.8, 55.6, 73.1, 127.5, 128.5, 128.7, 131.8, 134.2, 136.6, 160.7, 172.3. IR ($CHCl_3$): 3520, 3440, 1735, 1635 cm^{-1}. $[\alpha]_{20}^{D}$: +19 [(*c* 0.2 $CHCl_3$), lit.[13c]: −23 for *ent*-**18**].

(2*S*,4*S*,1′*S*,2′*S*)-2-(2-Azido-1-hydroxy-3-phenylpropyl)-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester 19. Sodium azide (0.976 g, 15 mmol) and water (5 mL) were successively added to a solution of epoxyoxazolidine *ent*-**7g** (0.265 g, 0.75 mmol) and ammonium chloride (0.803 g, 15 mmol) in EtOH (20 mL). The mixture was refluxed for 15 days and concentrated. Water was then added, and the resulting mixture was extracted with ether. The combined organic layers were dried ($MgSO_4$). After evaporation, azido alcohol **19** was isolated as a yellow oil (0.288 g, 97%) and used crude for the next step: ^{1}H NMR: 1.11 (t, J = 7.1 Hz, 3H), 2.99 (s, 1H), 3.02 (d, J = 2.3 Hz, 1H), 3.78 (m, 1H), 3.98 (m, 1H), 4.06 (dd, J = 4.1 and 8.9 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 4.25 (dd, J = 6.8 and 8.9 Hz, 1H), 4.9−5.3 (bs, 1H), 4.9 (dd, J = 4.2 and 6.7 Hz, 1H), 5.27 (d, J = 7.5 Hz, 1H), 7.15−7.3 (m, 10H); ^{13}C NMR: 14.4, 34.9, 60.4, 62.8, 65.6, 73.8, 76.3, 90.9, 126.3, 126.7, 128.0, 128.6, 128.9, 129.4, 138.2, 139.7, 156.8. IR ($CHCl_3$): 3300, 2105, 1695 cm^{-1}. $[\alpha]_{20}^{D}$: −4 (*c* 0.7 $CHCl_3$). Anal. Calcd for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10; N, 14.13. Found: C, 63.70; H, 6.13; N, 14.04.

(2*S*,4*S*,1′*S*,2′*S*)-2-[2-[*N*-(*tert*-Butoxycarbonyl)amino]-1-hydroxy-3-phenylpropyl]-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (20). A solution of azido alcohol **19** (0.3 g, 0.76 mmol) and di-*tert*-butyl dicarbonate (0.319 g, 1.46 mmol) in AcOEt (4 mL) was injected into a hydrogenation flask containing a prehydrogenated suspension of 5% Pd on carbon (0.06 g) in AcOEt (4 mL). The hydrogenation was complete in 17 h. The catalyst was filtered on Celite, and the filtrate was evaporated. The compound **20** (0.25 g, 70%) was obtained pure after crystallization in PE: mp 169 °C. ^{1}H NMR: 1.07 (t, J = 7.1 Hz, 3H), 1.24 (s, 9H), 2.80 (dd, J = 10.1 and 13.8 Hz 1H), 2.95 (dd, J = 4.7 and 13.9 Hz, 1H), 3.85−3.95 (bm, 1H), 4.2−4.3 (m, 3H), 4.22 (dd, J = 6.9 and 8.9 Hz, 1H), 4.2−4.3 (bm, 1H), 4.6−5.2 (bm, 2H), 5.15 (d, J = 7.5 Hz, 1H), 7.1−7.4 (m, 11H); ^{13}C NMR: 14.4, 28.4, 35.0, 53.0, 60.7, 62.6, 73.8, 76.4, 79.0, 91.1, 126.2, 126.7, 127.9, 128.3, 128.8, 129.6, 138.6, 139.9, 155.2, 156.7. IR ($CHCl_3$): 3400, 1700, 1600 cm^{-1}. $[\alpha]_{20}^{D}$: −67.6 (*c* 0.5 $CHCl_3$). Anal. Calcd for $C_{26}H_{34}N_2O_6$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.43; H, 7.26; N, 5.75.

(2*S*,4*S*,1′*S*,2′*S*)-2-[2-[*N*-(*tert*-Butoxycarbonyl)amino]-1-[(*tert*-butyldimethylsilyl)oxy]-3-phenylpropyl]-4-phenyloxazolidine-3-carboxylic Acid Ethyl Ester (21). 2,6-Lutidine (0.248 mL, 2.12 mmol) and *tert*-butyldimethylsilyl triflate (0.4 mL 1.74 mmol) were successively added to a solution of alcohol **20** (0.5 g, 1.06 mmol) in CH_2Cl_2 (5 mL) at −80 °C. The mixture was stirred for 4 h at −40 °C and treated by water. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by flash chromatography (E/PE: 10/90) gave compound **21** (0.554 g, 90%) as a colorless oil. ^{1}H NMR: −0.18 (s, 3H), −0.08 (s, 3H), 0.83 (s, 9H), 1.2 (t, J = 7 Hz, 3H), 1.31 (s, 9H), 2.7 (dd, J = 10.2 and 14.5 Hz, 1H), 3.02 (dd, J = 4.5 and 14.5 Hz, 1H), 3.95−4.4 (m, 6H), 4.56 (bs, 1H), 5.14 (bt, J = 6.1 Hz, 1H), 5.37 (bd, J = 4.4 Hz, 1H), 7−7.3 (m, 8H), 7.4−7.5 (m, 2H); ^{13}C NMR: −5.0, −4.5, 14.5, 18.2, 26.0, 28.3, 34.7, 53.1, 60.6, 62.0, 71.6, 75.2, 78.8, 90.6, 126.1, 127.3, 127.6, 128.3, 128.5, 129.1, 138.5, 139.2, 155.1, 156.5. IR ($CHCl_3$): 3400, 1700 cm^{-1}; $[\alpha]_{20}^{D}$: −19 (*c* 0.3 $CHCl_3$). Anal. Calcd for $C_{32}H_{48}N_2O_6Si$: C, 65.72; H, 8.27; N, 4.79. Found: C, 65.64; H, 8.26; N, 4.82.

(2*S*,3*S*)-3-[*N*-(*tert*-Butoxycarbonyl)amino]-2-[(*tert*-butyldimethylsilyl)oxy]-4-phenylbutanal 22. A solution of 1.0 M diisobutyl aluminum hydride (2.5 mL, 2.5 mmol) in toluene was added to a solution of oxazolidine **21** (0.256 g, 0.5 mmol) in CH_2Cl_2 (10 mL) at −78 °C. The mixture was stirred for 3 h at −78 °C and then hydrolyzed by an ammonium chloride saturated aqueous solution. The resulting mixture was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (10 mL), and SiO_2 (4.8 g), water (0.58 mL), and oxalic acid (0.048 g) were successively added. The heterogeneous mixture was stirred for 20 h at rt and then filtered on Celite. The filtrate was evaporated, and the aldehyde **22** (0.093 g, 55%) was obtained after flash chromatography (cyclohexane/AcOEt: 10/90) as a solid: mp 95 °C. ^{1}H NMR: 0.03 (s, 6H), 0.92 (s, 9H), 1.13 (s, 9H), 2.6−2.8 (m, 2H), 4−4.25 (bm, 2H), 4.4−4.5 (bm, 1H), 7.1−7.3 (m, 5H), 9.31 (d, J = 1Hz, 2H); ^{13}C NMR: −5, −4.5, 18.3, 25.9, 28.4, 35.8, 54.2, 79.5, 79.8, 126.9, 128.6, 137.0, 155.0, 201.4; IR ($CHCl_3$): 3400, 1730, 1700 cm^{-1}. $[\alpha]_{20}^{D}$: -30 [(*c* 1.06 $CHCl_3$), lit.[18]: −31].

AM1 Calculations. The calculations on species **23** and **24** were carried out using the AM1 hamiltonian[31] as implemented in the AMPAC program version 4.0 QCPE No 527. The geometries were optimized by using the Davidson−Fletcher−Powell algorithm (FLEPO procedure) that minimizes the energy with respect to all internal coordinates.

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