Stereoselective Mannich-Type Reaction of an Acyclic Ketimine with a Substituted Chlorotitanium Enolate: Efficient Approach to D-*erythro*-α-Trifluoromethyl-β-hydroxyaspartic Units

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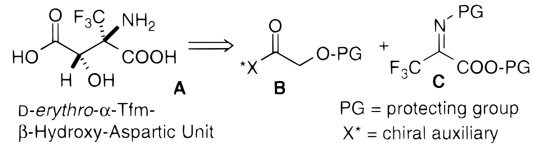
The sequence Arg-Gly-Asp (RGD) mediates binding of fibrinogen to its platelet receptors GP IIb/IIIa,[2] which represents a contributing factor in the platelet-mediated thrombus formation. Enormous interest has been devoted to the discovery of RGD analogues for an antithrombotic therapy.[3] In connection with a program for the synthesis of new RGD peptide mimetics incorporating α-trifluoromethyl (Tfm) α-amino acids,[4,5] as conformational modifiers, we needed to synthesize nonracemic α-Tfm-β-hydroxyaspartic acid units **A** in a stereoselective and effective manner.[6] Assembly of the chiral enolate **B** with the imine **C** was envisaged as a potentially convenient entry to **A** (Scheme 1).

This goal presented several stimulating challenges. First, to our knowledge no method has yet been reported for the synthesis of nonracemic units **A**. Second, very few examples of stereoselective addition of enolates to acyclic ketimines are extant in the literature, none of them involving substituted enolates.[7] Finally, the stereocontrolled synthesis of organofluorine compounds bearing a quaternary carbon is a mostly unresolved problem.[8]

Here, we disclose the synthesis of D-*erythro*-α-Tfm-β-hydroxyaspartic units, exploiting a highly stereoselective

Scheme 1



Mannich-type reaction of the chlorotitanium enolate of (α-benzyloxy)acetyl 2-oxazolidinone (*S*)-**1**[9,10] with the *N*-Cbz-imine of ethyl trifluoropyruvate **2a**[11] (Scheme 2).

Our choice to use the 2-oxazolidinone ring system as a chiral auxiliary was driven by its well-established application in synthesis, by its high versatility and ready

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(2) Samanen, J.; Ali, F.; Romoff, T.; Calvo, R.; Sorenson, E.; Vasko, J.; Storer, B.; Berry, D.; Bennett, D.; Strohsacker, M.; Powers, D.; Stadel, J.; Nichols, A. *J. Med. Chem.* **1991**, *34*, 3114.

(3) See, for example: McDowell, R. S.; Gadek, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 9245.

(4) Dal Pozzo, A.; Muzi, L.; Moroni, M.; Rondanin, R.; de Castiglione, R.; Bravo, P.; Zanda, M. *Tetrahedron* **1998**, *54*, 6019.

(5) (a) *Fluorine-containing Amino Acids: Synthesis and Properties*; Kukhar, V. P., Soloshonok, V. A., Eds.; Wiley: Chichester, 1994. (b) Koksch, B.; Sewald, N.; Jakubke, H.-D.; Burger, K. In *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; pp 42−58.

(6) It is worth noting that the D-*erythro*-α-Tfm-β-hydroxyaspartic unit **A** can be also envisaged as a suitable precursor of the polar head of the 2-Tfm-analogue of natural sphingosine, the structural unit common to most natural sphingolipids. For a review, see: Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, 1075. Efforts directed toward the total synthesis of D-*erythro*-2-Tfm-sphingosine are presently in progress.

(7) For some reviews: (a) Bloch, R. *Chem. Rev. (Washington, D.C.)* **1998**, *98*, 1407. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895. To our knowledge, the few existing examples are limited to stereoselective aldol reactions of acyclic *N*-sulfinylketimines with enolates of acetate: (c) Davis, F. A.; Reddy, R. T.; Reddy, R. E. *J. Org. Chem.* **1992**, *57*, 6387. (d) Tang, T. P.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 12. For leading references on asymmetric condensations of enolates with aldimines, see: (e) Abrahams, I.; Motevalli, M.; Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1994**, *50*, 12755. (f) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron Lett.* **1993**, *34*, 6921. (g) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Ponzini, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 2939. (h) Annunziata, R.; Benaglia, M.; Chiovato, A.; Cinquini, M.; Cozzi, F. *Tetrahedron* **1995**, *51*, 10025. (i) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 5821. (j) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1994**, *50*, 9471. (k) Boger, D. L.; Honda, T. *Tetrahedron Lett.* **1993**, *34*, 1567. (l) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909. (m) Vaccaro, W. D.; Sher, R.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 35. (n) Fujisawa, T.; Ichikawa, M.; Ukaji, Y.; Shimizu, M. *Tetrahedron Lett.* **1993**, *34*, 1307. (o) Evans, D. A.; Morrissey, M. M.; Dorow, R. L. *J. Am. Chem. Soc.* **1985**, *107*, 4346. (p) van der Steen, F. H.; Kleijn, H.; Britovsek, G. J. P.; Jastrzebski, J. T. B. H.; van Koten, G. *J. Org. Chem.* **1992**, *57*, 3906. (q) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287. (r) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227. (s) Hart, D. J.; Lee, C.-S. *J. Am. Chem. Soc.* **1986**, *108*, 6054.

(8) (a) Bravo, P.; Crucianelli, M.; Vergani, B.; Zanda, M. *Tetrahedron Lett.* **1998**, *39*, 7771. (b) Ishii, A.; Miyamoto, F.; Higashiyama, K.; Mikami, K. *Tetrahedron Lett.* **1998**, *39*, 1199. (c) Sewald, N.; Seymour, L. C.; Burger, K.; Osipov, S. N.; Kolomiets, A. F.; Fokin, A. V. *Tetrahedron: Asymmetry* **1994**, *5*, 1051. (d) Zanda, M.; Bravo, P.; Volonterio, A. In *Asymmetric Fluoro-Organic Chemistry: Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society Symposium Series; American Chemical Society: Washington, DC, 1999; in press.

(9) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

(10) (a) Evans, D. A.; Gage, J. R.; Leighton, J. L.; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961 and references therein. For leading references on aldol reactions involving α-alkoxy-acetyloxazolidinones, see: (b) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506. (c) Keck, G. E.; Palani, A.; McHardy, S. F. *J. Org. Chem.* **1994**, *59*, 3113. (d) Batchelor, M. J.; Gillespie, R. J.; Golec, J. M. C.; Hedgecock, C. J. R.; Jones, S. D.; Murdoch, R. *Tetrahedron* **1994**, *50*, 809. (e) Fuhry, M. A. M.; Holmes, A. B.; Marshall, D. R. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2743. (f) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. (g) Evans, D. A.; Kaldor, S. V.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (h) Piscopio, A. D.; Minowa, N.; Chakraborty, T. K.; Koide, K.; Bertinato, P.; Nicolaou, K. C. *J. Chem. Soc., Chem. Commun.* **1993**, 617. (i) Ku, T. W.; Kondrad, K. H.; Gleason, J. G. *J. Org. Chem.* **1989**, *54*, 3487. (j) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* **1984**, 753. (k) Miyata, O.; Shinada, T.; Ninomiya, I.; Naito, T. *Tetrahedron* **1997**, *53*, 2421. (l) Andrus, M. B.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 10420. (m) Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434. (n) Evans, D. A.; Barrow, J. C.; Leighton, J. L.; Robichaud, A. J.; Sefkow, M. *J. Am. Chem. Soc.* **1994**, *116*, 12111. (o) Loubinoux, B.; Sinnes, J.-L.; O'Sullivan, A. C.; Winkler, T. *Helv. Chim. Acta* **1995**, *78*, 122. (p) Martin, S. F.; Dodge, J. A.; Burgess, L. E.; Limberakis, C.; Hartmann, M. *Tetrahedron* **1996**, *52*, 3229. (q) Hulin, B.; Newton, L. S.; Lewis, D. M.; Genereux, P. E.; Gibbs, E. M.; Clark, D. A. *J. Med. Chem.* **1996**, *39*, 3897. (r) Roush, W. R.; Marron, T. G.; Pfeifer, L. A. *J. Org. Chem.* **1997**, *62*, 474. (s) Crimmins, M. T.; Choy, A. L. *J. Org. Chem.* **1997**, *62*, 7548.

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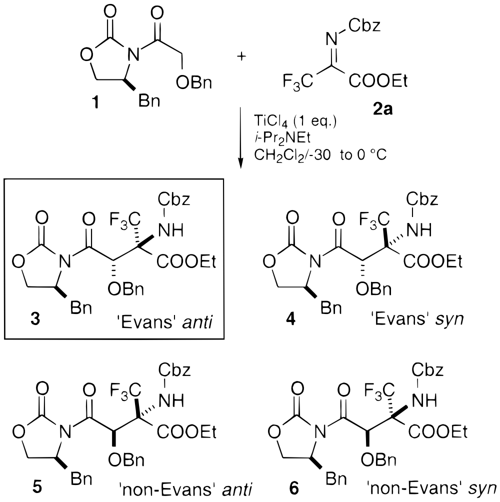
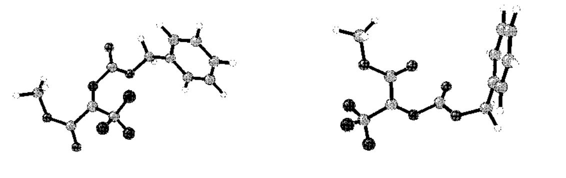
Scheme 2



availability in both enantiomeric forms from unexpensive parent amino acids.[12] The strongly electrophilic imine **2a** was prepared *in situ* by Staudinger reaction of the iminophosphorane $Ph_3P{=}NCbz$[13] with 1 equiv of commercial ethyl trifluoropyruvate and used without removing the coproduct Ph_3PO.

In an effort to obtain a stereoselective C−C bond formation, we initially explored the lithium enolate of **1**. Unfortunately, a 65:35 mixture of "non-Evans"-*anti* and -*syn* adducts **5** and **6**, respectively, was produced in modest yields (47%).[14] Even more disappointingly, and somewhat surprisingly, repeated attempts to form and react a boron enolate of **1** (Bu_2BOTf−i-Pr_2NEt−CH_2Cl_2), a tin (IV) enolate ($SnCl_4$−i-Pr_2NEt−CH_2Cl_2), or a tin(II) enolate [$Sn(OTf)_2$−Et_3N−CH_2Cl_2] did not lead to any adduct **3**−**6**.

Finally, we investigated the chlorotitanium enolate of **1** [$TiCl_4$ (1 equiv), i-Pr_2NEt, CH_2Cl_2, −30 °C]. Satisfactorily, the "Evans"-*anti* adduct **3** and the minor "non-Evans" *anti*-**5** were produced in a 91:9 ratio (88% overall isolated yield) after 2 h at 0 °C, while *syn*-**4**,**6** were not detected at all in the crude mixture.[15] The use of Et_3N instead of i-Pr_2NEt afforded lower stereoselectivity (**3**:**5**:**4**:**6** = 79:21:0:0, 70%). Next, we examined the use of 2 equiv of $TiCl_4$, since its stoichiometry has been reported to exert remarkable influence in related processes.[16] In this case, the identical ratio **3**:**5**:**4**:**6** = 91:9:0:0 was obtained, although in much lower yields (ca. 30%). Precomplexation of the imine **2a** with 1 equiv of $TiCl_4$ afforded yields lower than 5%.[17] Ph_3PO, which is present in the reaction environment using *in situ* generated imine **2a**, has no effect on the stereoselectivity. In fact, the use of Ph_3PO-free imine **2a**, obtained by selective extraction in boiling *n*-hexane, did not produce any detectable variation of the diastereomeric ratio (**3**:**5**:**4**:**6** = 91:9:0:0, 70%).



(*Z*)-**2** (*E*)-**2**

Figure 1. HF/6-31G*-optimized structures of (*Z*)- and (*E*)-**2b**.

To understand the source of the high, and rather unexpected, stereoselectivity for this Mannich-type reaction, we investigated the geometry of the imine **2a**. As judged by ^1H and ^{19}F NMR spectroscopy ($CDCl_3$, rt), **2a** exists as a single geometric isomer, probably the thermodynamic one, since imines derived from fluorinated ketones can interconvert rapidly at ambient temperatures.[18] However, for the same reason, the presence of a single set of signals could be due to a fast equilibrium between *E* and *Z* forms or to an accidental overlap of the signals. The exceeding reactivity of **2a** precluded the use of analytical techniques such as TLC or HPLC. Thus, we decided to evaluate the relative energies of the *Z* and *E* isomers of *N*-Cbz-imines of trifluoropyruvate performing *ab initio* MO calculations. The methyl ester **2b** was used as a model.

The structures (*Z*)-**2b** and (*E*)-**2b** were fully optimized by Hartree−Fock calculations with the 6-31G* basis set.[19] The optimized structures are shown in Figure 1. The *Z* isomer was calculated to be 10.3 kcal mol^{-1} less stable than the *E* isomer,[20] which adopts a slightly nonplanar *s-cis* conformation, featuring a significant twisting of the *N*-Cbz carbonyl with respect to the CO_2Me group. This twisting is probably caused by the electrostatic repulsion between the carbonyl oxygen lone pairs. Imines **2a**,**b** should therefore exist only as (*E*)-geometric isomers, having the stereoelectronically demanding CF_3 *trans* with respect to the Cbz.

The TS leading to the major adduct **3** should involve electrophilic addition of (*E*)-**2a** from its *Si*-face to the unhindered *Si*-face of the (*Z*)-chlorotitanium enolate of (*S*)-**1**. The Evans facial diastereoselectivity of the title reaction strongly suggests that titanium is not coordinated to the oxazolidinone carbonyl at the time of the electrophilic attack. On the other hand, the total *anti* simple diastereoselection provides evidence for efficient coordination of the electrophile (*E*)-**2a**. Thus, the stereochemical outcome might be rationalized using the model **D** featuring complexation of both the spatially close

(11) (a) Bravo, P.; Capelli, S.; Meille, S. V.; Viani, F.; Zanda, M.; Kukhar, V. P.; Soloshonok, V. A. *Tetrahedron*: *Asymmetry* **1994**, *5*, 2009.

(12) Gage, J. R.; Evans, D. A. *Org. Synth.* **1989**, *68*, 77−91.

(13) Kricheldorf, H. R. *Synthesis* **1972**, 695.

(14) The low yields were due to partial decomposition of lithium enolate of **1**, probably *via* fragmentation into α-benzyloxyketene and the corresponding deacylated *N*-lithium 2-oxazolidinone.

(15) Diastereomeric ratios established by ^{19}F NMR and HPLC.

(16) See, for example: (a) Walker, M. A.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 5747. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883.

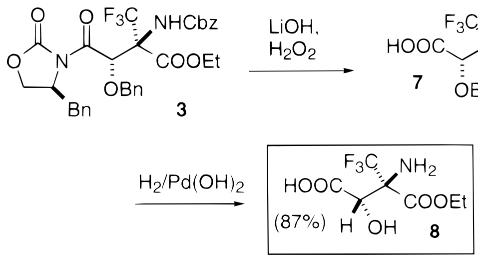
(17) The byproducts formed by $TiCl_4$ precomplexation of **2** were not investigated.

(18) Osipov, S. N.; Kolomiets, A. F.; Fokin, A. V. *Russ. Chem. Rev.* **1992**, *61*, 798.

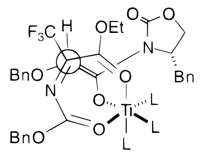
(19) Gaussian 94, Revision C.3: Frisch, M. J.; Schlegel, G. W.; Trucks, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, N.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andrés, J. L., Replogle, E. S.; Gomperts, R.; Martín, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Head-Gordon, M.; González, C.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1995.

(20) The preferential *anti* geometry of the *N*-substituent with respect to the fluorinated rest in **2** has been already observed in related structures. See, for example: Fustero, S.; Navarro, A.; Pina, B.; Asensio, A.; Bravo, P.; Crucianelli, M.; Volonterio, A.; Zanda, M. *J. Org. Chem.* **1998**, *63*, 6210.

Scheme 3



carbonyl oxygens of (*E*)-**2a** by titanium, within its expanded coordination sphere.



D

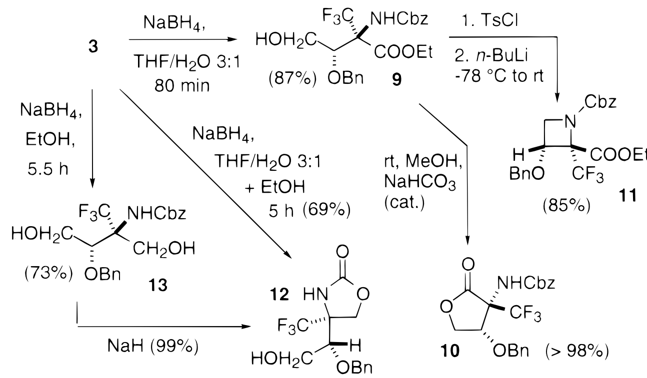
Imine nitrogen is believed to be not involved in the coordination, because of its exceedingly poor Lewis basicity.[21] This theory is supported by the literature. In fact, Iseki and Kobayashi reported that aldol reactions of boron and titanium acyloxazolidinone enolates with fluoral and hexafluoroacetone, which do not undergo coordination, take place with totally reverse non-Evans facial selectivity and moderate *anti* simple selectivity.[22]

Aldol adduct **3** is a versatile intermediate for the synthesis of D-*erythro*-α-Tfm-β-hydroxyaspartic acid **8** (Scheme 3) and several derivatives (Scheme 4).

The acyloxazolidinone imide bond was hydrolyzed in exocyclic fashion with LiOOH[23] to provide protected α-Tfm-β-hydroxy-aspartate **7** (Scheme 3). Simultaneous catalytic hydrogenolysis of both *N*-Cbz and *O*-Bn groups delivered the target α-Tfm derivative **8**.

To prepare reduced derivatives of **8** from **3**, we have developed a new epimerization-free, chemoselective, and fine-tunable method for the exocyclic reductive removal of the 2-oxazolidinone ring. $NaBH_4$ in a mixture of THF

Scheme 4



and protic solvents (EtOH and/or H_2O) was used for this purpose.[24] In contrast, the conventional reagents $LiAlH_4$ or $LiBH_4$ produced low chemoselectivity and/or low yields of the desired oxazolidinone-free products (Scheme 4). Thus, treatment of **3** with 16 equiv of $NaBH_4$ in a mixture of THF/H_2O 3:1 at −20 °C for ca. 2 h afforded the diastereomerically pure carbinol D-*erythro*-**9** in excellent yields, without affecting the COOEt. The chiral auxiliary (*S*)-4-Bn-2-oxazolidinone was recovered quantitatively. D-*Erythro*-α-Tfm-α-NHCbz-γ-lactone **10** was quantitatively prepared by cyclization of **9**. Selective transformation of **9** into the corresponding primary tosylate, followed by intramolecular cyclization (*n*-BuLi, −78 °C, rt), produced a high yield of the azetidine **11**.

The cyclic carbamate **12** was prepared from **3** by one-pot reductive oxazolidinone cleavage/COOEt reduction/intramolecular cyclization, achieved with 5 equiv of $NaBH_4$ in a mixture of THF/H_2O 3:1 + 5% EtOH. Esterification of **12** with (+)-(*S*)-α-methoxyphenylacetic acid provided a compound suitable for X-ray diffraction, which allowed us to establish the absolute configuration of **3** and derivatives.[25]

The diol D-*erythro*-**13** was obtained from **3** upon reductive oxazolidinone cleavage/COOEt reduction (8 equiv of $NaBH_4$, absolute EtOH, 0 °C, 5.5 h). The minor aldol adduct **5** was analogously treated, providing the enantiomer L-*erythro*-**13**, that allowed us to assess the stereochemistry of **5**. By action of NaH, D-*erythro*-**13** provided the carbamate **12** as well (quantitative).

In summary, a rare example of stereoselective Mannich-type reaction of a ketimine with a substituted enolate has been disclosed, optimized and exploited for the synthesis of enantiomerically pure, densely functionalized D-*erythro*-α-trifluoromethyl-β-hydroxy-aspartic units.

Experimental Section

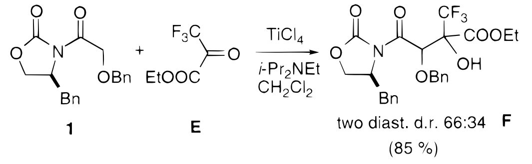
For general experimental information see ref 20.

Synthesis of Imine 2a. To a solution of $Ph_3P{=}NCbz$[13] (440 mg, 1.07 mmol) in dry THF (6 mL) was added a solution of ethyl trifluoropyruvate **E** (190 mg, 1.12 mmol) in dry THF (2 mL) at room temperature, under nitrogen. The solution was warmed at 50 °C for 10 min and then stirred at room temperature for 2 h; finally, the solvent was removed in vacuo.

2-Benzyloxycarbonylimino-3,3,3-trifluoropropionic acid ethyl ester (2a): ^1H NMR ($CDCl_3$) δ 7.70−7.34 (5H, m), 5.33

(21) Three strongly electron-withdrawing groups, namely CF_3, COOEt, and COOBn, attached to the C=N bond render the nitrogen lone pair unavailable to coordination by Lewis acids and the imine carbon strongly electrophilic: see ref 18.

(22) (a) Iseki, K.; Oishi, S.; Taguchi, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 8147. (b) Makino, Y.; Iseki, K.; Fujii, K.; Oishi, S.; Hirano, T.; Kobayashi, Y. *Tetrahedron Lett.* **1995**, *36*, 8147. Those reactions were proposed to take place *via* open TS involving chelated acyloxazolidinone enolates. It is worth noting that almost identical non-Evans-*anti* stereocontrol was described for the reactions of lithium, boron, and titanium enolates of chiral acyloxazolidinones with several fluorine-free pyruvic esters: (c) Jacobson, I. C.; Reddy, G. P. *Tetrahedron Lett.* **1996**, *37*, 8263. For the sake of comparison, ethyl trifluoropyruvate **E** was also reacted with the chlorotitanium enolate of **1**, using the identical optimized conditions found for the parent imine **2a**.



As expected, the reaction afforded a mixture of two diastereomeric adducts **F** (whose stereochemistry has not been determined yet) with low stereocontrol (66:34 ratio, 85%). For very recent impressive progress in the field of enantiocontrolled aldol reactions of pyruvates see: (d) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. V. *J. Am. Chem. Soc.* **1999**, *121*, 686.

(23) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(24) To our knowledge, the use of $NaBH_4$ to achieve reductive removal of 2-oxazolidinone rings from *N*-acyloxazolidinones had not been reported yet in the literature. However, while this manuscript was in preparation, a paper describing the use of $NaBH_4$ in THF/water for achieving the same transformation appeared: Prashad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.

(25) X-ray data will be published separately.

(2H, s), 4.31 (2H, q, $J = 7.15$ Hz), 1.31 (3H, t, $J = 7.15$ Hz); ^{19}F NMR ($CDCl_3$) δ − 71.4 (s); ^{13}C NMR ($CDCl_3$) δ 167.7, 154.6, 135.1, 132.0, 128.6, 121.4 (q, $J = 287.6$ Hz), 69.6, 64.3, 13.7.

Mannich-Type Reaction with $TiCl_4$. To a cooled solution of **1** (87 mg, 0.27 mmol) in dry CH_2Cl_2 (1.5 mL) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (0.27 mL, 0.27 mmol) at − 30 °C under nitrogen atmosphere. After 10 min, Hunig's base (0.09 mL, 0.54 mmol) was added, and the resulting dark purple solution was stirred at the same temperature for 1 h. Then, a solution of crude **2a** (85 mg, 0.28 mmol) in dry CH_2Cl_2 (1 mL) was added *via* cannula. The solution was slowly warmed to 0 °C, and after 3 h, the reaction was quenched with saturated aqueous $NaHCO_3$, filtered on a Celite pad, and extracted with CH_2Cl_2. The collected organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (FC) (75:25 hexane/AcOEt) afforded 148 mg of pure diastereoisomers **3** and **5** in a 91:9 ratio (88% overall yield).

Mannich-Type Reaction with LDA. To a cooled solution of **1** (221 mg, 0.68 mmol) in dry THF (2 mL) was added a 1.5 M solution of LDA in THF (0.48 mL, 0.71 mmol) at −78 °C under nitrogen atmosphere. After 15 min, a solution of **2a** (215 mg, 0.71 mmol) in dry THF (2 mL) was added at the same temperature. After 1 h, the solution was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The collected organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (95:5 benzene/AcOEt) afforded 201 mg of a 65:35 mixture of diastereoisomers **5** and **6** (47% overall yield).

(2*R*,3*S*)-4-[(4*S*)-4-Benzyl-2-oxooxazolidin-3-yl]-3-benzyloxy-2-benzyloxycarbonylamino-4-oxo-2-trifluoromethylbutyric acid ethyl ester (3): R_f (7:3 hexane/AcOEt) 0.38; $[\alpha]^{20}_D$ +11.2 (*c* 0.96, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.13 (15H, m), 6.37 (1H, s), 6.03 (1H, s), 5.16 (1H, d, $J = 12.1$ Hz), 5.01 (1H, d, $J = 12.1$ Hz), 4.66 (1H, d, $J = 11.4$ Hz), 4.65 (1H, m), 4.48 (1H, d, $J = 11.4$ Hz), 4.12 (2H, q, $J = 7.1$ Hz), 4.10 (2H, m), 3.12 (1H, dd, $J = 13.4, 3.7$ Hz), 2.42 (1H, dd, $J = 13.4, 10.1$ Hz), 1.26 (3H, t, $J = 7.1$ Hz); ^{19}F NMR ($CDCl_3$) δ − 69.5 (3F, s); ^{13}C NMR ($CDCl_3$) δ 167.5, 164.2, 154.3, 153.5, 135.6, 134.9, 129.2, 129.0, 128.7, 128.55, 128.50, 128.4, 128.1, 128.0, 127.4, 125.2, 123.3 (q, $J = 288.9$ Hz), 77.2, 73.7, 73.2, 67.4 (q, $J = 27.6$ Hz), 67.0, 63.4, 55.8, 38.0, 13.4; MS (EI, 70 eV) *m/z* 629 (M^+, 7), 431 (11), 304 (14), 181 (29), 91 (100); FT IR (cm^{-1}) 3422, 1784, 1738, 1502; HRMS (FAB) calcd for ($M^+ + 1$) $C_{32}H_{32}F_3N_2O_8$ 629.2111, found 629.2113.

(2*S*,3*R*)-4-[(4*S*)-4-Benzyl-2-oxooxazolidin-3-yl]-3-benzyloxy-2-benzyloxycarbonylamino-4-oxo-2-trifluoromethylbutyric acid ethyl ester (5): R_f (7:3 hexane/AcOEt) 0.45; $[\alpha]^{20}_D$ +24.0 (*c* 0.87, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.16 (15H, m), 6.47 (1H, s), 5.81 (1H,s), 5.15 (1H, d, $J = 12.5$ Hz), 5.04 (1H, d, $J = 12.5$ Hz), 4.77 (1H, d, $J = 11.5$ Hz), 4.70 (1H, m), 4.44 (1H, d, $J = 11.5$ Hz), 4.17 (2H, m), 4.02 (1H, dd, $J = 8.8, 1.9$ Hz), 3.80 (1H, dd, $J = 8.8$ Hz both), 3.46 (1H, dd, $J = 13.8, 3.1$ Hz), 2.48 (1H,dd, $J = 13.8, 11.1$ Hz), 1.30 (3H, t, $J = 7.1$ Hz); ^{19}F NMR ($CDCl_3$) δ − 69.7 (3F, s); ^{13}C NMR ($CDCl_3$) δ 167.2, 164.0, 154.5, 153.0, 135.7, 129.6, 129.4, 128.9, 128.6, 128.56, 128.47, 128.39, 128.1, 128.0, 127.2, 127.0, 123.4 (q, $J = 288.5$ Hz), 74.1, 72.4, 66.7, 63.4, 55.8, 36.6, 29.7, 13.6, CF_3 signal is obscured due to its low intensity.

(2*R*,3*R*)-4-[(4*S*)-4-Benzyl-2-oxooxazolidin-3-yl]-3-benzyloxy-2-benzyloxycarbonylamino-4-oxo-2-trifluoromethylbutyric acid ethyl ester (6): R_f (7:3 hexane/AcOEt) 0.30; $[\alpha]^{20}_D$ + 26.9 (*c* 0.39, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.11 (15H, m), 6.76 (1H, s), 6.12 (1H, s), 5.17 (1H, d, $J = 12.2$ Hz), 5.10 (1H, d, $J = 12.2$ Hz), 4.80 (1H, d, $J = 11.8$ Hz), 4.52 (1H, d, $J = 11.8$ Hz), 4.32 (3H, m), 4.03 (1H, dd, $J = 9.1, 3.3$ Hz), 3.90 (1H, dd, $J = 9.1$ Hz both), 3.24 (1H, dd, $J = 13.3, 3.1$ Hz), 2.46 (1H, dd, $J = 13.3, 10.2$ Hz), 1.27 (3H, t, $J = 6.9$ Hz); ^{19}F NMR ($CDCl_3$) δ −69.2 (3F, s); ^{13}C NMR ($CDCl_3$) δ 167.9, 163.2, 154.4, 153.2, 136.2, 134.6, 130.9, 129.3, 129.0, 128.7, 128.5, 128.33, 128.29, 128.24, 128.21, 127.4, 123.3 (q, $J = 288.9$ Hz), 74.4, 73.2, 67.3, 66.6, 63.0, 55.3, 42.0, 37.3, 13.8, CF_3 signal is obscured due to its low intensity.

Synthesis of 7. To a cooled solution of **3** (286 mg, 0.45 mmol) in a 4:1 mixture of THF/H_2O (5 mL) was added a 30% (in weight) aqueous solution of H_2O_2 (0.19 mL, 1.82 mmol) at 0 °C under nitrogen atmosphere, followed by solid LiOH (11 mg, 0.45 mmol). After 90 min, the reaction was quenched with saturated aqueous Na_2SO_3, warmed to room temperature, and extracted twice with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (from 1:1 hexane/AcOEt to 1:1 hexane/AcOEt + 1% AcOH) afforded 162 mg of **7** (76%) and quantitative recovery of the oxazolidinone.

(2*R*,3*S*)-3-Benzyloxy-2-benzyloxycarbonylamino-2-trifluoromethylsuccinic acid 1-ethyl ester (7): R_f (1:1 hexane/AcOEt + 1% of AcOH) 0.21; $[\alpha]^{20}_D$ −17.2 (*c* 0.98, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40−7.14 (10H, m), 6.38 (1H, br s), 5.10 (2H, s), 4.77 (1H, d, $J = 11.0$ Hz), 4.60 (1H, s), 4.49 (1H, d, $J = 11.0$ Hz), 4.20 (2H, m), 2.36 (1H, s), 1.20 (3H, t, $J = 7.1$ Hz); ^{19}F NMR ($CDCl_3$) δ −70.4 (3F, s); ^{13}C NMR ($CDCl_3$) δ 171.8, 163.4, 154.1, 135.6, 135.5, 129.0, 128.5, 128.4, 128.3, 128.0, 123.4 (q, $J = 288.5$ Hz), 74.1, 70.2, 67.7, 66.4 (q, $J = 28.6$ Hz), 63.1, 13.6; FT IR (cm^{-1}) 2926, 1748, 1506; HRMS (FAB) calcd for ($M^+ + 1$) $C_{22}H_{23}F_3NO_7$ 470.1427, found 470.1428.

Synthesis of 8. To a stirred solution of **7** (158 mg, 0.34 mmol) in absolute MeOH (6 mL) was added a catalytic amount of Pd-$(OH)_2$/C, and the slurry was vigorously stirred for 2 h at room temperature, under dihydrogen atmosphere. $Pd(OH)_2$/C was removed by filtration on a Celite pad, and the solution was concentrated in vacuo. The crude was washed with CH_2Cl_2, affording 72 mg (87%) of **8** as a white solid.

(2*R*,3*S*)-2-Amino-3-hydroxy-2-trifluoromethylsuccinic acid 1-ethyl ester (8): R_f (8:1:1 *t*-BuOH/AcOH/H_2O) 0.40; $[\alpha]^{20}_D$ +15.6 (*c* 0.65, MeOH); ^{1}H NMR (CD_3OD) δ 4.30 (2H, q, $J = 7.0$ Hz), 3.31 (1H, br s), 1.30 (3H, t, $J = 7.0$ Hz); ^{19}F NMR (CD_3OD) δ −71.1 (3F, s); ^{13}C NMR (CD_3OD) δ 172.4, 166.0, 124.8 (q, $J = 285.8$ Hz), 72.3, 68.3 (q, $J = 26.6$ Hz), 64.5, 14.0; MS (EI, 70 eV) *m/z* 246 ($M^+ + 1$, 100), 200 (14), 170 (53), 142 (32); FT IR (cm^{-1}) 2954, 2855, 1762, 1655.

Synthesis of (+)-9. To a suspension of $NaBH_4$ (223 mg, 5.90 mmol) in a 3:1 mixture of THF/H_2O (4 mL) was added a solution of **3** (370 mg, 0.59 mmol) in THF (1.9 mL) dropwise at − 20 °C. After 25 min, 3 equiv of solid $NaBH_4$ was added at −20 °C, followed by other 3 equiv after 1 h at the same temperature. The reaction was quenched with saturated aqueous NH_4Cl, warmed to room temperature, and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (7:3 hexane/AcOEt) afforded 233 mg of (+)-**9** (87%) and the quantitative recovery of the oxazolidinone. The same procedure was applied for the synthesis of the enantiomer (−)-**9** starting from **5** (83% yield and quantitative recovery of the oxazolidinone).

(+)-(2*R*,3*S*)-3-Benzyloxy-2-benzyloxycarbonylamino-4-hydroxy-2-trifluoromethylbutyric acid ethyl ester (9): R_f (8:2 hexane/AcOEt) 0.22; $[\alpha]^{20}_D$ +3.0 (*c* 1.05, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37−7.13 (10H, m), 6.28 (1H, s), 5.13 (1H, d, $J = 12.1$ Hz), 5.06 (1H, d, $J = 12.1$ Hz), 4.67 (1H, d, $J = 11.1$ Hz), 4.60 (1H, d, $J = 11.1$ Hz), 4.23 (3H, m), 3.84 (1H, dd, $J = 12.0, 6.1$ Hz), 3.74 (1H, dd, $J = 12.0, 5.0$ Hz), 2.15 (1H, br s), 1.25 (3H, t, $J = 7.1$ Hz); ^{19}F NMR ($CDCl_3$) δ − 68.7 (3F, s); ^{13}C NMR ($CDCl_3$) δ 164.7, 154.4, 136.8, 135.8, 128.6, 128.5, 128.3, 128.0, 123.9 (q, $J = 288.5$ Hz), 78.7, 74.3, 67.6 (q, $J = 26.8$ Hz), 67.4, 63.0, 61.2, 13.8; MS (EI, 70 eV) *m/z* 456 ($M^+ + 1$, 11), 410 (27), 274 (87), 181 (23), 91 (100); FT IR (cm^{-1}) 3468, 1751, 1703, 1460; HRMS (FAB) calcd for ($M^+ + 1$) $C_{22}H_{25}F_3NO_6$ 456.1634, found 456.1635.

(−)-(2*S*,3*R*)-3-Benzyloxy-2-benzyloxycarbonylamino-4-hydroxy-2-trifluoromethylbutyric acid ethyl ester 9: $[\alpha]^{20}_D$ −2.7 (*c* 0.75, $CHCl_3$); R_f, ^{1}H, ^{13}C, ^{19}F NMR, MS, and FT IR spectra matched those of (+)-**9**.

Synthesis of 10. To a solution of (+)-**9** (23 mg, 0.05 mmol) in MeOH (0.5 mL) was added a catalytic amount of saturated aqueous $NaHCO_3$, and the resulting solution was stirred at room temperature for 10 min. The reaction was quenched with saturated aqueous NH_4Cl and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (85:15 hexane/AcOEt) allowed quantitative recovery of the lactone **10** (21 mg).

(4*S*,3*R*)-(4-Benzyloxy-2-oxo-3-trifluoromethyltetrahydrofuran-3-yl)carbamic acid benzyl ester (10): R_f (8:2 hexane/AcOEt) 0.42; $[\alpha]^{20}_D$ −1.2 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.37−7.22 (10H, m), 5.55 (1H, br s), 5.14 (1H, d, $J = 12.3$ Hz), 5.07 (1H, d, $J = 12.3$ Hz), 4.65 (1H, d, $J = 11.3$ Hz), 4.60 (1H, m), 4.51 (1H, d, $J = 11.3$ Hz), 4.47 (1H, dd, $J = 10.0$, 5.6 Hz), 4.27 (1H, m); ^{19}F NMR ($CDCl_3$) δ −75.0 (3F, s); ^{13}C NMR ($CDCl_3$) δ 154.7, 136.3, 129.8, 128.7, 128.6, 128.5, 128.4, 128.3, 127.9, 122.8 (q, J = 285.8 Hz), 72.3, 73.5, 71.7, 69.3, 68.0, CF_3 signal is obscured due to its low intensity; MS (EI, 70 eV) m/z 410 (M^+, 1), 274 (27), 196 (6), 91 (100); FT IR (cm^{-1}) 2926, 1799, 1729; HRMS (FAB) calcd for (M^+ + 1) $C_{20}H_{19}F_3NO_5$ 410.1215, found 410.1228.

Synthesis of 11. To a solution of **9** (97 mg, 0.21 mmol) in dry CH_2Cl_2 (3.5 mL) were added triethylamine (0.033 mL, 0.23 mmol) and solid TsCl (48.7 mg, 0.25 mmol) at room temperature under nitrogen atmosphere. After 14 h, the solution was quenched with water and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (8:2 hexane/AcOEt) afforded 110 mg of *O*-tosylate (85%). To a solution of *O*-tosylate (28 mg, 0.05 mmol) in dry THF (0.5 mL) was added dropwise a 2.5 M solution of *n*-BuLi in hexane (0.02 mL, 0.05 mmol) at −78 °C and under nitrogen atmosphere. The mixture was slowly warmed until 0 °C. After 4 h, the reaction was quenched with saturated aqueous NH_4Cl, warmed to room temperature, and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (8:2 hexane/AcOEt) afforded 20 mg of **11** (85%).

(2*R*,3*R*)-3-Benzyloxy-2-trifluoromethylazetidine-1,2-dicarboxylic acid 1-benzyl ester 2-ethyl ester (11): R_f (8:2 hexane/ethyl acetate) 0.45; $[\alpha]^{20}_D$ −34.6 (*c* 0.97, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.44−7.29 (10H, m), 5.30 (1H, d J = 12.0 Hz), 5.23 (1H, d J = 12.0 Hz), 4.70 (1H, d J = 11.7 Hz), 4.65 (1H, d J = 11.7 Hz), 4.32−4.25 (4H, m), 3.96 (1H, dd J = 13.2, 2.8 Hz), 1.29 (3H, t J = 7.2 Hz); ^{19}F NMR ($CDCl_3$) δ −72.0 (3F, s); ^{13}C NMR ($CDCl_3$) δ 167.8, 153.8, 136.8, 135.8, 128.5, 128.4, 128.3, 128.1, 127.8, 123.3 (q, J = 284.8 Hz), 72.3, 69.9, 69.1, 68.6 (q, J = 26.8 Hz), 65.1, 63.1, 13.9; MS (EI, 70 eV) m/z 437 (M^+, 9), 212 (19), 181 (26), 91 (100); FT IR (cm^{-1}) 1752, 1677, 1401; HRMS (FAB) calcd for (M^+ + 1) $C_{22}H_{23}F_3NO_5$ 438.1528, found 438.1524.

Synthesis of 12 from 3. To a cooled solution of **3** (194 mg, 0.31 mmol) in a 3:1 mixture of THF/H_2O was added solid $NaBH_4$ (35 mg, 0.93 mmol) at 0 °C. After 1 h, another 2 equiv of solid $NaBH_4$ (23 mg) was added. After 4 h, the solution was diluted with EtOH (1 mL) and stirred for 30 min at room temperature. The reaction was quenched by carefully adding saturated aqueous NH_4Cl and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (1:1 hexane/AcOEt) afforded 65 mg of **12** (69%) and quantitative recovery of the oxazolidinone.

(4*S*)-4-[(1*S*)-1-Benzyloxy-2-hydroxyethyl)]-4-trifluoromethyloxazolidin-2-one (12): R_f (1:1 hexane/AcOEt) 0.30; $[\alpha]^{20}_D$ −22.1 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.42−7.28 (5H, m), 6.85 (1H, br s), 4.71 (1H, d, J = 11.3 Hz), 4.65 (1H, d, J = 11.3 Hz), 4.61 (1H, d, J = 9.8 Hz), 4.44 (1H, d, J = 9.8 Hz), 3.92 (1H, m), 3.77 (1H, dd, J = 16.8, 3.7 Hz), 3.76 (1H, m), 1.79 (1H, br s); ^{19}F NMR ($CDCl_3$) δ − 78.4 (3F, s); ^{13}C NMR ($CDCl_3$) δ 158.8, 136.6, 128.7, 128.4, 128.1, 124.7 (q, J = 285.8 Hz), 77.9, 74.1, 66.7, 65.2 (q, J = 28.7 Hz), 60.5; MS (EI, 70 eV) m/z 611 ($2M^+$, 19), 396 (M^+ + CH_2Ph, 27), 306 (M^+ + 1, 14), 91 (100); FT IR (cm^{-1}) 3278, 1761. HRMS (FAB) calcd for (M^+ + 1) $C_{13}H_{15}F_3NO_4$ 306.0953, found 306.0964.

Synthesis of 13. To a solution of **3** (614 mg, 0.98 mmol) in dry EtOH (9.8 mL) was added 5 equiv of solid $NaBH_4$ (185 mg) at 0 °C. The reaction appeared very slow by TLC monitoring. Thus, after 3 h another 3 equiv of solid $NaBH_4$ (111 mg) was added at the same temperature. After 5 h, the reaction was quenched by adding carefully saturated aqueous NH_4Cl (gas evolution), warmed to room temperature, and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (1:1 hexane/AcOEt) afforded 295 mg of **13** (73%) and the quantitative recovery of the oxazolidinone.

(1*S*,2*S*)-(2-Benzyloxy-3-hydroxy-1-hydroxymethyl-1-trifluoromethylpropyl)carbamic acid benzyl ester (13): R_f (6:4 hexane/ethyl acetate) 0.42; $[\alpha]^{20}_D$ +15.7 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.38−7.28 (10H, m), 5.84 (1H, br s), 5.13 (1H, d J = 12.3 Hz), 5.07 (1H, d J = 12.3 Hz), 4.64 (1H, d J = 11.2 Hz), 4.58 (1H, d J = 11.2 Hz), 4.10−3.82 (3H, m), 3.72 (1H, dd J = 11.4, 2.7 Hz), 2.70 (2H, br signal); ^{19}F NMR ($CDCl_3$) δ − 75.9 (3F, s); ^{13}C NMR ($CDCl_3$) δ 156.3, 136.7, 135.5, 128.65, 128.59, 128.51, 128.3, 128.2, 125.5 (q, J = 289.4 Hz), 78.9, 73.5, 67.6, 63.8 (q, J = 25.0 Hz), 60.2, 59.5; MS (EI, 70 eV) m/z 307 (M^+ − OCH_2Ph, 1), 289 (45), 246 (21), 91 (100); FT IR (cm^{-1}) 3409, 1720, 1510, 1455.

Synthesis of 12 from 13. To a suspension of NaH (80% in weight, 18 mg, 0.58 mmol) in dry THF (1 mL) was added a solution of **13** (142 mg, 0.34 mmol) in a 3:1 mixture of dry THF/DMF (4 mL) dropwise at 0 °C under nitrogen atmosphere. After 20 min, the reaction was quenched with water, warmed to room temperature, and extracted with AcOEt. The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by FC (1:1 hexane/AcOEt) afforded 104 mg of **12** (quantitative).

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Supporting Information Available: Copies of optimized structures at the HF/6-31G* level for compounds (*Z*)- and (*E*)-**2b** and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of (2*R*,3*S*)-**3**, (2*R*,3*S*)-**7**, (2*R*,3*S*)-**8**, (2*R*,3*S*)-**9**, (3*R*,4*S*)-**10**, (2*R*,3*R*)-**11**, **12**, and (1*S*,2*S*)-**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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