Highly Diastereoselective Conjugate Addition of Carbon Nucleophiles to a Chiral Oxygenated α,β-Unsaturated δ-Lactone. A Straightforward Synthesis of Functionalized Branched-Chain L-Sugars†

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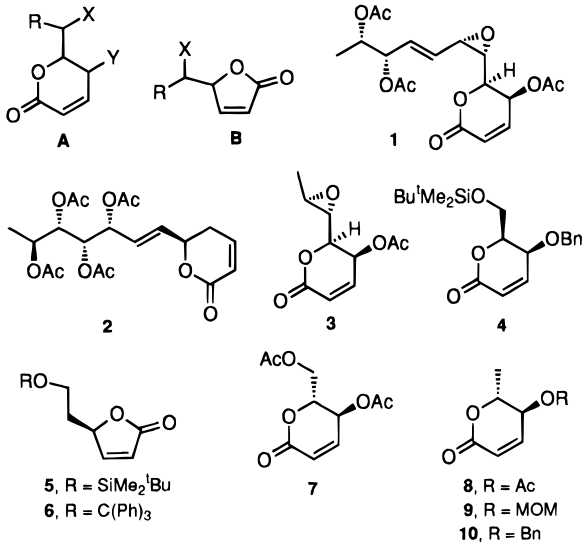
Received August 9, 1995

Highly functionalized chiral, enantiomerically pure, molecules are useful intermediates for the EPC synthesis[1] of natural products and pharmacologically active compounds.[2] The stereocontrolled synthesis of these chiral building blocks is an important objective in organic chemistry.

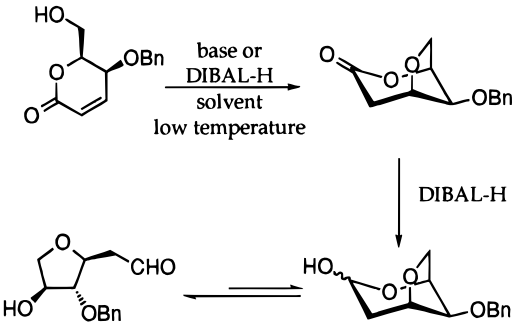
A suitable template for achieving this goal is an enantiomerically pure functionalized unsaturated lactone (e.g., **A** and **B**, Chart 1). The electrophilic double bond in these molecules can serve as a reactive center to obtain higher functionalized chiral building blocks through conjugate addition of suitable nucleophiles.[3] It is known[4] that the kinetic nucleophilic conjugate addition is under stereoelectronic control; if this feature is combined with a conformational bias in the template lactones **A** and **B**, a highly diastereoselective conjugate addition is expected.

In the course of our work on the synthesis of cytotoxic natural products having polyoxygenated α,β-unsaturated-δ-lactone structures, such as (+)-olguine (**1**, Chart 1),[5] (+)-anamarine (**2**),[6] and (+)-asperlin (**3**)[7] and analogues, we have developed efficient routes to the oxygenated α,β-unsaturated γ- and δ-lactones **4**−**10** (Chart 1), which involve either the lactonization of the corresponding hydroxy unsaturated ester[8] or the oxidation of glycals.[9]

Chart 1



Scheme 1



Although a likely mechanism of the biological activity of these natural products is through the conjugate addition of a nucleophilic biomolecule, it is surprising that the stereocontrolled addition to oxygenated α,β-unsaturated δ-lactones has been scarcely studied.[10]

We have previously observed the smooth conjugate addition of heteronucleophiles to these compounds[11] and found that, whereas the intermolecular reaction goes with poor stereocontrol,[12] the intramolecular addition is highly diastereoselective, affording chiral tetrahydrofurans (for an example, see Scheme 1).

Stereocontrolled carbon−carbon bond formation is a major goal in modern synthetic methodology. Conjugate addition of carbon nucleophiles is an important tool to achieve this objective.[3] In this paper, we report our results on the highly diastereoselective conjugate addition of both dialkyl cuprates and soft nucleophiles to the

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(1) EPC-synthesis: synthesis of enantiomerically pure compound. For a definition and discussion, see: Seebach, D.; Hungerbühler, E. In *Modern Synthetic Methods*; Scheffold, R, Ed.; Salle and Sauerländer: Berlin, 1980; Vol. 2, pp 93−171.

(2) Hanessian, S. *The Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, 1983. Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: Orlando, 1984; Vol. 4, pp 1−226.

(3) (a) Oare, D. A.; Heathcock, C. H. *Top. Stereochem.* **1989**, *19*, 227−407. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: New York 1991; Vol. 4, Chapters 1.1−1.6, pp 1−268. (c) Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1992.

(4) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983. Herradón, B.; Seebach, D. *Helv. Chim. Acta* **1989**, *72*, 690−714 and references cited therein.

(5) Valverde, S.; Herradón, B.; Rabanal, R. M.; Martín-Lomas, M. *Can. J. Chem.* **1987**, *65*, 332−338. Valverde, S.; Martín-Lomas, M.; Herradón, B. *J. Carbohydr. Chem.* **1987**, *6*, 685−690.

(6) Valverde, S.; Hernández, A.; Herradón, B.; Rabanal, R. M.; Martín-Lomas, M. *Tetrahedron* **1987**, *43*, 3499−3504.

(7) Valverde, S.; Herradón, B.; Rabanal, R. M.; Martín-Lomas, M. *Can. J. Chem.* **1987**, *65*, 339−342.

(8) (a) Valverde, S.; Herradón, B.; Martín-Lomas, M. *Tetrahedron Lett.* **1985**, *26*, 3731−3734. (b) Herradón, B. *Tetrahedron: Asymmetry* **1991**, *2*, 191−194.

(9) Sánchez-Sancho, F.; Herradón, B. Manuscript in preparation. See also: Lichtenthaler, F. W.; Rönninger, S.; Jarglis, P. *Liebigs Ann. Chem.* **1989**, 1153−1161.

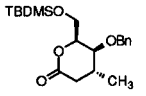
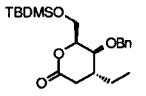
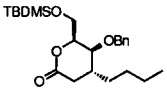
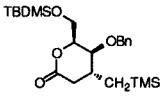
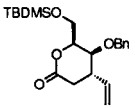
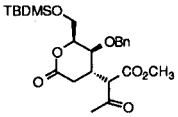
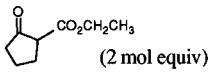
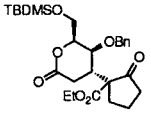
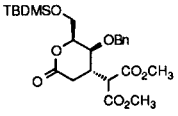
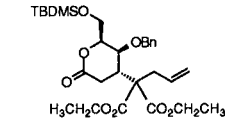
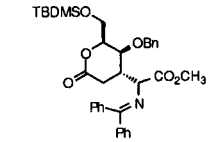
(10) To the best of our knowledge, the only reported example of stereocontrolled conjugate addition of carbon nucleophiles to this kind of molecules is the addition of a benzyllithium reagent to an oxygenated α,β-unsaturated δ-lactone as a step in the synthesis of olivin trimethyl ether; see: Franck, R. W.; Bhat, V.; Subramanian, C. S. *J. Am. Chem. Soc.* **1986**, *108*, 2455−2457. On the other hand, the conjugate addition to α,β-unsaturated γ-lactones and alkyl-substituted α,β-unsaturated δ-lactones have been more extensively studied; for a survey of the literature, see pp 283−297 in ref 3c.

(11) Herradón, B. Ph. D. Dissertation, Universidad Complutense, Madrid, 1986. García-Ochoa, S. Ph. D. Dissertation, Universidad Autónoma, Madrid, 1988.

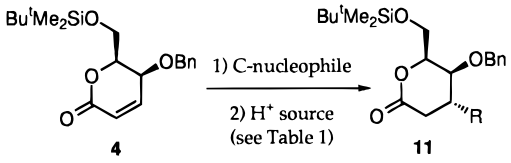
(12) The lack of stereocontrol in the intermolecular reaction must be due to partial epimerization of the initially formed product through a retro-Michael addition.

0022-3263/96/1961-1143$12.00/0

Table 1. Results of the Michael Addition of Carbon-nucleophiles to the Lactone 4

Entry	Experimental Conditions	Product (Yield)
1	Me_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O, -20°, 22 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	 **11a** (90%)
2	$Et_2CuMgBr$ (4 mol equiv) TMSCl (10 mol equiv) Et_2O/THF (3:1), -20°, 20 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	 **11b** (63%)
3	Bu_2CuLi (4 mol equiv) TMSCl (10 mol equiv) Et_2O/Hexane (4:1), -20°, 24 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	 **11c** (83%)
4	$(TMSCH_2)_2CuLi$ (4 mol equiv) TMSCl (10 mol equiv) Et_2O/pentane (3:1), -20°, 20 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	 **11d** (92%)
5	$(CH_2{=}CH)_2CuMgBr$ (4 mol equiv) TMSCl (10 mol equiv) Et_2O/THF (3:1), -20°, 24 hours; $NH_3/NH_4Cl/H_2O$, -20° to r. t.	 **11e** (55%)
6	$CH_3COCH_2CO_2CH_3$ (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 3.5 hours; NH_4Cl/H_2O, 0° to r. t.	 **11f** (74%)
7	 (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 4 hours; NH_4Cl/H_2O, 0° to r. t.	 **11g** (98%)
8	$CH_2(CO_2CH_3)_2$ (2 mol equv) $KOBu^t$ (2 mol equiv) THF, r. t., 3.5 hours; NH_4Cl/H_2O, 0° to r. t.	 **11h** (63%)
9	$(CH_2{=}CH\text{-}CH_2)CH(CO_2CH_2CH_3)_2$ (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 8 hours; NH_4Cl/H_2O, 0° to r. t.	 **11i** (69%)
10	$Ph_2C{=}NCH_2CO_2CH_3$ (2 mol equiv) $KOBu^t$ (2 mol equiv) THF, r. t., 4 hours; NH_4Cl/H_2O, 0° to r. t.	 **11k** (70%)

Scheme 2



readily available[8a] chiral α,β-unsaturated δ-lactone **4** (Scheme 2). The structural and stereochemical features of the lactone **4** forecast a highly stereoselective, kinetically-controlled, addition with carbon nucleophiles. Furthermore, from a stereochemical point of view, the lactone **4** is formally a sugar of the, not easily, accesible L-series.[13] Because the Michael addition works efficiently, the procedure constitutes a straightforward way to prepare functionalized branched-chain sugars of the L-series, which are constituents of a variety of biologically active natural products. Interestingly, with soft nucleophilic anions from β-diketones, Claisen condensations instead of conjugate additions are observed (Scheme 3, and see below).

The results of the conjugate additions of carbon nucleophiles to the lactone **4**, as well as some experimental details, are indicated in Table 1.

Several features deserve comment:

(13) (a) For recent syntheses of L-sugars, see: Ford, M. J.; Ley, S. V. *Synlett* **1990**, 771−772. Giuliano, R. M.; Villani, F. J., Jr. *J. Org. Chem.* **1995**, *60*, 202−211. (b) For recent syntheses of branched-chain sugars, see: Toshima, K.; Yoshida, T.; Mukaiyama, S.; Tatsuta, K. *Tetrahedron Lett.* **1991**, *32*, 4139−4142. Yanagihara, R.; Osanai, S.; Yoshikawa, S. *Chem. Lett.* **1992**, 89−90. (c) For a review of earlier work, see: McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125−188.

(a) In all the cases examined, the facial diastereoselectivity[14] of the addition to the lactone ring has been total;[15] giving the products **11a**−**k** in moderate to excellent isolated yields. The nucleophiles attack on the (3-*si*,4-*re*) face of the olefinic bond. The evidence has been obtained by careful analysis of the ^{1}H-NMR spectra of both the crude and purified materials (see below).

(b) Both alkyllithium and Grignard reagents are useful for generating dialkyl cuprates using copper(I) iodide as a copper source (entries 1−5, Table 1). The reaction with dialkylcuprates must be carried in the presence of trimethylsilyl chloride.[16] In the absence of trimethylsilyl chloride, the reactions are very sluggish, and only low yields of the addition products have been obtained. Under these conditions, the reaction products, compounds **11a**−**e**, have been single diastereoisomers.

(c) In order to obtain good yields of conjugate addition products, it has been necessary to use 4 molar equiv of dialkyl cuprate; lower amounts have given slower reactions.

(d) Although it is known[17] that the conjugate addition of Grignard reagents can be carried out with catalytic amounts of copper(I) salt, this procedure has resulted in low yields in our hands, and a 2:1 molar ratio of alkylmagnesium bromide to copper(I) iodide is necessary to achieve reasonable conversions and rates (entries 2 and 5, Table 1).

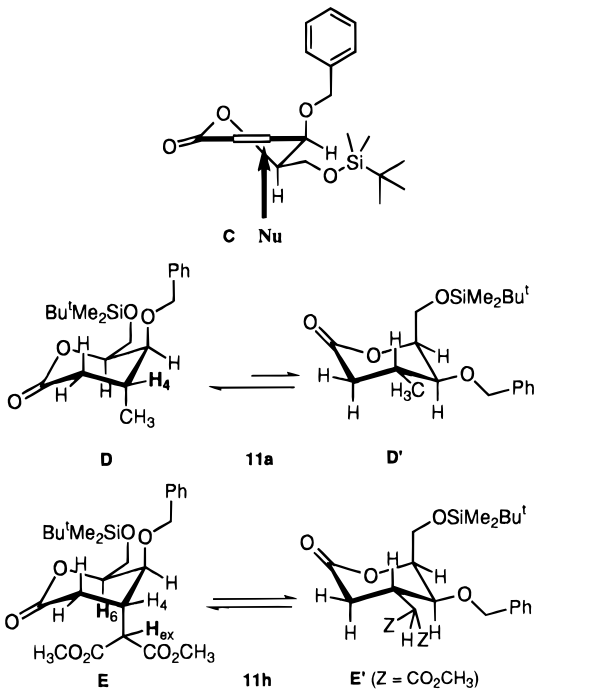
(e) A variety of soft carbon nucleophiles has been used, giving the Michael addition products **11f**−**k** (entries 6−10, Table 1). These nucleophiles include the anions generated from β-keto esters (entries 6 and 7, Table 1), malonates (entry 8, Table 1), α-substituted malonates (entry 9), and activated glycine derivatives[18] (entry 10, Table 1).

(f) Although the facial steroselectivity of attack to the olefinic bond of the unsaturated lactone **4** is total;[15] a *ca.* 1:1 inseparable mixture of epimers has been obtained when a new exocyclic stereogenic center is formed (compounds **11f**, **11g**, and **11k**, entries 6, 7, and 10, Table 1).[19] That the two isomers of each compound are epimeric in the exocyclic carbon has been deduced from the analysis of the coupling pattern in the ^{1}H-NMR spectrum of the protons H-3 and H-4 in the two epimers of the tetrahydro-2-pyranones **11f**, **11g**, and **11k** (see below).

(g) The dense functionality of compounds **11f**−**k** makes them suitable chiral building blocks for further synthetic applications. Some targets include fused heterocyclic systems, such as lactones and cyclic ethers, from compounds **11f**−**i**, and kainoids, and peptide−lactone hybrids,[20] from the glycine derivative **11k**.

Although the steric course of the addition to the most populated and most reactive conformation[21] of **4** (see **C**, Chart 2) can be anticipated on the basis of steric (*trans*-addition to the substituents on the ring) as well as stereoelectronic (axial attack[4]) grounds,[22] the stereochemistry has been confirmed by careful analysis of the ^{1}H-NMR spectrum of **11a** (see **D**) and a NOESY experiment on **11h** (see **E**, Chart 2).

Chart 2



The most significant data on the ^{1}H-NMR spectrum of **11a** are the coupling constants between H-3 and H-4: J (H-3$_{ax}$−H-3$_{eq}$) = 17. 1 Hz; J (H-3$_{ax}$−H-4) = 6.6 Hz; and J (H-3$_{eq}$−H-4) = 5.3 Hz, which indicates that H-4 is not axial, **D** being the most populated conformer of compound **11a** (Chart 2).[23]

The most significant data from the NOESY spectrum of **11h** are the existence of NOE between the proton H-6 and the proton at the exocyclic position (H$_{ex}$ in structure **E**, Chart 2) and the absence of NOE between H-4 and H-6. The coupling constants between H-3 and H-4 in the ^{1}H-NMR spectrum of **11h** [7.0 and 8.5 Hz] point out that, contrary to **11a**, there is not a preferred conformation in compound **11h**, which exists as a mixture of rapidly equilibrating conformers (**E** and **E′**, Chart 2), and this fact reflects the higher steric demand of the voluminous substituent in C-4 of the tetrahydro-2-pyranone ring.

All the products **11a**−**k** from conjugate additions to lactone **4** present the same coupling pattern of H-3 and H-4 in the ^{1}H-NMR spectrum as that of **11a** or **11h**, which denotes the same stereochemical course in additions to the olefinic double bond.

(14) The diastereoselectivities have been determined by careful analysis of ^{1}H- and ^{13}C-NMR spectra.

(15) For a definition, see: Seebach, D.; Zimmermann, J.; Gysel, U.; Ziegler, R.; Ha, T. K. *J. Am. Chem. Soc.* **1988**, *110*, 4763−4772.

(16) Nakamura, E. In *Organocopper Reagents. A Practical Approach*; Taylor, R. J. K., Ed.; Oxford University Press: Oxford, 1994; pp 129−142.

(17) Erdik, E. *Tetrahedron* **1984**, *40*, 641−657.

(18) O'Donnell, M. J.; Polt, R. L. *J. Org. Chem.* **1982**, *47*, 2663−2666.

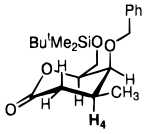
(19) Along with the two epimers, a small amount of the enol tautomer of **10f** has been detected in $CDCl_3$ solution (^{1}H-NMR evidence).

(20) Herradón, B.; Fenude, E. Manuscript in preparation. See also: Liskamp, R. M. J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 305−307.

(21) Leonard, J.; Ryan, G.; Swain, P. A. *Synlett* **1990**, 613−614. Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1985**, *26*, 6015−6018 and references cited therein.

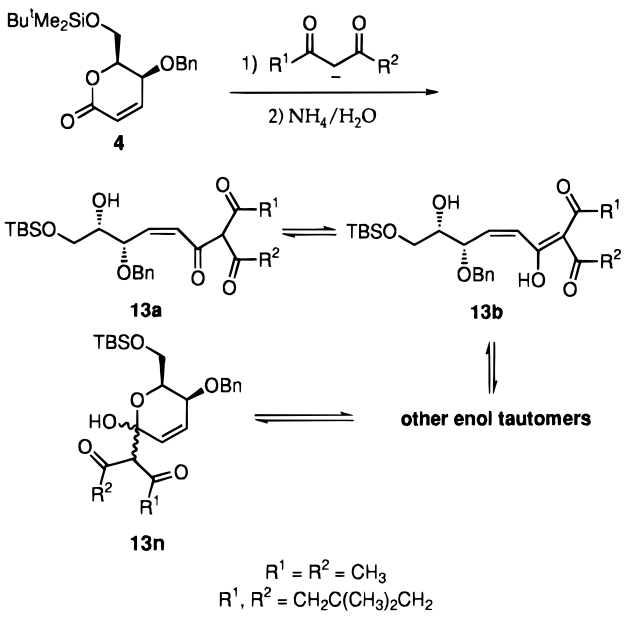
(22) Very preliminary results on the conjugate addition to the lactones **9** and **10** (see Chart 1) seem to indicate that stereoelectronic factors are more important than steric influences in determining the stereochemical outcome of the Michael addition of dialkyl cuprates. Sánchez-Sancho, F.; Herradón, B. Manuscript in preparation.

(23) The epimer of **11a** (namely, **12**) is expected to have the conformation indicated below, where H-4 is axially oriented.



12

Scheme 3



As has been pointed out above, a different reaction takes place with soft nucleophiles from β-diketones. Thus, when the α,β-unsaturated-δ-lactone **4** is treated with either the potassium or sodium salts of pentane-1,3-dione or dimedone,[24] no Michael addition product is detected in the crude material and only the products of Claisen condensations are observed (compound **13**, Scheme 3). The absence of conjugate addition products is apparent by analysis of the ^{1}H-NMR spectrum; especially significant is the absence of the characteristic ABX system of H-3 and H-4 in the Michael addition products (see above and Experimental Section); the formation of Claisen condensation products **13** is denoted by the presence of olefinic protons in the region 6.0−6.4 ppm, with vicinal coupling constants of *ca.* 12 Hz, which indicates the presence of a α,β-unsaturated carbonyl compound with *Z*-configuration. Although the reaction products of both reactions have been single spots on TLC (hexane/ethyl acetate, 7:3), both ^{1}H-NMR and ^{13}C-NMR spectra are relatively complex, indicating the existence of several tautomeric forms in the reaction product (**13a**−**n**, Scheme 3). Even the cyclic tautomers **13n** are detected, as minor components, by peaks at 104.3 and 103.0 ppm in the ^{13}C-NMR spectra of the products of the reactions of both pentane-1,3-dione and dimedone with the lactone **4**. To the best of our knowledge, this different behavior (Claisen condensation *versus* Michael addition, depending on the nature of the nucleophile) of a α,β-unsaturated carbonyl compound with soft nucleophiles has not been previously reported. Currently, we are carrying out studies on the generality of the distinct reactivities of the anions of β-diketones as compared with other soft nucleophiles.

In summary, the conjugate additions of carbon nucleophiles to the chiral, enantiomerically pure, α,β-unsaturated δ-lactone **4** are highly diastereoselective, and provide efficient routes to the synthesis of some densely functionalized chiral building blocks (**11**). Further synthetic applications of these compounds, as well as studies on the origin of the diastereoselectivity are currently underway.

(24) The reactions have been carried out at room temperature in THF, using either NaH or KOBu^t to generate the carbanion, following a procedure analogous to the reported in the Experimental Section for the conjugate addition of active methylene compounds.

Experimental Section[25]

Conjugate Addition of Lithium or Bromomagnesium Dialkylcuprates to the α,β-Unsaturated δ-Lactone 4. General Procedure for the Synthesis of 11a−e. A solution of the organolithium or Grignard reagents (8 mmol)[26] was added dropwise to a slurry of CuI (760 mg, 4 mmol) in diethyl ether (12 mL) at 0 °C under argon atmosphere. After the mixture was stirred for 10 min, the copper reagent was treated with Me_3-SiCl (1.3 mL, 10 mmol). After the mixture was cooled at −20 °C, a solution of the α,β-unsaturated δ-lactone **4** (348 mg, 1.0 mmol) in diethyl ether (6 mL) was added. The reaction mixture was stirred at −20 °C for the time indicated in Table 1 (entries 1−5). After this time, the reaction was quenched by the addition of 6 mL of a NH_3/NH_4Cl solution (pH 8). The mixture was diluted with diethyl ether, the phases were separated, the aqueous phase was extracted with diethyl ether (twice), and the combined organic extracts were washed with water and brine and dried over $MgSO_4$. Evaporation of the solvent gave the crude material, which was further purified by flash chromatography,[27] to give pure compounds **11a**−**e** in the isolated yields indicated in Table 1. The spectroscopic (*J* values given in Hz) and analytical data of the tetrahydro-2-pyranones **11a**−**f** are indicated below.

(4*R*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-methyltetrahydro-2-pyranone (11a): $[\alpha]_D$ −13.6° (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.65 (d, *J* = 11.7, 1H), 4.54 (d, *J* = 11.7, 1H), 4.39 (ddd, *J* = 2.7, 5.3, 7.1, 1H), 3.93 (dd, *J* = 7.1, 10.1, 1H), 3.87 (dd, *J* = 5.3, 10.1, 1H), 3.57 (dd, *J* = 2.7, 4.2, 1H), 2.82 (dd, *J* = 6.6, 17.1, 1H), 2.41 (distorted ddd, *J* = 4.2, 5.3, 6.6, 1H), 2.20 (dd, *J* = 5.3, 17.1, 1H), 1.08 (d, *J* = 7.1, 3H), 0.89 (s, 9H), 0.076 (s, 3H), 0.071 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 170.5 (s), 137.7 (s), 128.3 (2C, d), 127.8 (d), 127.5 (2C, d), 78.3 (d), 75.1 (d), 71.7 (t), 60.9 (t), 34.3 (t), 29.4 (d), 25.8 (3C, q), 18.6 (q), 18.2 (s), −5.5 (q), −5.6 (q); MS *m/e* 365 (0.4), 364 (0.05, M^+), 215 (2.4), 117 (2.5), 99 (2.6), 91 (100), 73 (6.0), 65 (3.2). Anal. Calcd for $C_{20}H_{32}O_4Si$: C, 65.93; H, 8.79. Found: C, 66.21; H, 9.02.

(4*R*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-ethyltetrahydro-2-pyranone (11b): $[\alpha]_D$ −14.2° (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.65 (d, *J* = 11.8, 1H), 4.53 (d, *J* = 11.8, 1H), 4.32 (distorted ddd, *J* = 2.1, 5.4, 7.3, 1H), 3.93 (dd, *J* = 7.1, 9.9, 1H), 3.85 (dd, *J* = 5.5, 9.9, 1H), 3.67 (broad distorted t, *J* ≈ 2.9, 1H), 2.80 (dd, *J* = 6.3, 16.5, 1H), 2.24 (dd, *J* = 5.7, 16.5, 1H), 2.22−2.11 (m, 1H), 1.30 (m, 2H), 0.96 (t, *J* = 7.4, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.00 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 170.9 (s), 137.8 (s), 128.4 (2C, d), 127.8 (d), 127.6 (2C, d), 78.6 (d), 73.6 (d), 71.5 (t), 60.8 (t), 36.5 (t), 32.4 (d), 26.0 (t), 25.8 (3C, q), 18.2 (s), 11.3 (q), −5.4 (q), −5.5 (q); MS *m/e* 379 (M + 1, 0.08), 321 (1.3), 229 (1.9), 215 (2.0), 117 (7.2), 113 (2.2), 105 (2.1), 92 (10.2), 91 (100), 89 (5.3), 75 (8.6), 73 (5.2), 65 (3.8), 59 (3.6), 57 (6.8), 55 (3.1), 43 (2.0), 41 (5.1). Anal. Calcd for $C_{21}H_{34}O_4Si$: C, 66.62; H, 9.05. Found: C, 66.99; H, 8.65.

(4*R*,5*S*,6*S*)-5-(Benzyloxy)-4-butyl-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]tetrahydro-2-pyranone (11c): $[\alpha]_D$ −11.5° (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.38−7.27 (m, 5H), 4.64 (d, *J* = 11.7, 1H), 4.53 (d, *J* = 11.7, 1H), 4.33 (ddd, *J* = 2.2, 5.4, 7.4, 1H), 3.92 (dd, *J* = 7.4, 10.1, 1H), 3.85 (dd, *J* = 5.4, 10.1, 1H), 3.64 (m, 1H), 2.79 (dd, *J* = 8.2, 18.5, 1H), 2.24 (dd, *J* = 5.4, 18.5, 1H), 2.23−2.19 (m, 1H), 1.43−1.23 (m, 6H), 0.89 (s, 9H), 0.88 (t, *J* = 6.7, 3H), 0.07 (s), −0.08 (s); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 170.8 (s), 137.7 (s), 128.4 (2C, d), 127.8 (d), 127.5 (2C, d), 78.5 (d), 73.7 (d), 71.5 (t), 60.8 (t), 34.6 (d), 32.7 (t), 32.6 (t), 28.8 (t), 25.8 (3C, q), 22.5 (t), 18.1 (s), 13.9 (q), −5.5 (q), −5.6 (q); MS *m/e* 407 (0.5), 406 (M^+, 0.04), 349 (1.5) 149 (1.8),

(25) For a general experimental procedure, see: Herradón, B.; Valverde, S. *Tetrahedron: Asymmetry* **1994**, *5*, 1479−1500.

(26) MeLi (1.5 M) in Et_2O, EtMgBr (3.0 M) in Et_2O, *n*-BuLi (1.45 M) in hexane, Me_3SiCH_2Li (1.0 M) in pentane, and 1.0 M vinylmagnesium bromide in THF were used for generating the copper reagent.

(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−5.

141 (1.9), 117 (3.4), 101 (2.0), 92 (10.5), 91 (100), 89 (3.1), 75 (6.1), 73 (5.8). Anal. Calcd for $C_{23}H_{38}O_4Si$: C, 67.94; H, 9.42. Found: C, 68.18; H, 9.39.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-[(trimethylsilyl)methyl]tetrahydro-2-pyranone (11d): $[\alpha]_D$ −7.8° (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.66 (d, *J* = 11.5, 1H), 4.58 (d, *J* = 11.5, 1H), 4.48 (ddd, *J* = 2.5, 5.3, 7.7, 1H), 3.98−3.80 (m, 2H), 3.58 (m, 1H), 2.89 (dd, *J* = 6.2, 17.0, 1H), 2.40−2.32 (m, 1H), 2.22 (dd, *J* = 4.0, 17.0, 1H), 0.91 (s, 9H), 0.14−0.01 (m, 2H), 0.08 (s, 3H), 0.03 (s, 9H), 0.01 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 170.4 (s), 137.8 (s), 128.4 (2C, d), 127.8 (d), 127.6 (2C, d), 78.1 (d), 75.3 (d), 71.9 (t), 60.8 (t), 34.6 (t), 30.8 (d), 25.8 (3C, q), 20,9 (t), 18.2 (s), −1.0 (3C, q), −5.5 (q), −5.6 (q); MS *m*/*e* 437 (M+1, 0.2), 379 (1.2), 365 (1.1), 171 (1.4), 149 (1.8), 147 (3.5), 117 (3.6), 99 (2.0), 91 (100), 73 (34.2), 41 (5.7). Anal. Calcd for $C_{23}H_{40}O_4Si_2$: C, 63.25; H, 9.23. Found: C, 63.50; H, 9.41.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-vinyltetrahydro-2-pyranone (11e): $[\alpha]_D$ −4.1° (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37−7.30 (m, 5H), 5.80 (distorted ddd, *J* = 6.2, 10.7, 17.1, 1H), 5.23 (dd, *J* = 1.0, 10.7, 1H), 5.17 (dd, *J* = 1.5, 17.1, 1H), 4.69 (d, *J* = 11.7, 1H), 4.58 (d, *J* = 11.7, 1H), 4.35 (ddd, *J* = 2.4, 5.3, 7.7, 1H), 3.91 (dd, *J* = 7.7, 10.0, 1H), 3.83 (dd, *J* = 5.3, 10.0, 1H), 3.74 (dd, *J* = 2.6, 4.2, 1H), 3.04−2.99 (m, 1H), 2.86 (dd, *J* = 6.6, 17.3, 1H), 2.52 (dd, *J* = 4.4, 17.3, 1H), 0.89 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 169.9 (s), 137.6 (s), 136.7 (d), 128.5 (2C, d), 127.9 (d), 127.6 (2C, d), 117.3 (t), 78.7 (d), 73.3 (d), 71.9 (t), 60.8 (t), 38.3 (d), 30.6 (t), 25.8 (3C, q), 18.2 (q), −5.4 (q), −5.5 (q); MS *m*/*e* 376 (M^+, 0.04), 361 (0.05), 117 (3.5), 92 (11.7), 91 (100), 89 (3.3), 73 (6.8), 65 (3.1), 59 (2.1), 57 (1.7). Anal. Calcd for $C_{21}H_{32}O_4Si$: C, 66.98; H, 8.57. Found: C, 67.36; H, 8.80.

Conjugate Addition of Active Methylene/methyne Compounds to the α,β-Unsaturated δ-Lactone 4. General Procedure for the Synthesis of 11f−k. A solution of the active methylene/methyne compound (2.0 mmol) in THF (5 mL) was dropwise added to a suspension of $KOBu^t$ (224 mg, 2.0 mmol) in THF (5 mL) at room temperature under argon atmosphere. The colored solution was stirred for 45 min at room temperature and treated with a solution of the α,β-unsaturated δ-lactone **4** (348 mg, 1.0 mmol) in THF (6 mL). After being stirred at room temperature for the time indicated in Table 1 (entries 6−10), the reaction mixture was cooled at 0 °C and quenched with saturated aqueous NH_4Cl (15 mL). The mixture was diluted with Et_2O; the phases were separated; the aqueous one was extracted with Et_2O (twice), and the combined organic extracts were washed with brine and dried ($MgSO_4$). All the volatiles were removed under vacuum to give a crude material, which was further purified by flash chromatography[27] to give compounds **11f−k** in the isolated yields indicated in Table 1 (entries 6−10). The spectroscopic and analytical data of the tetrahydro-2-pyranones **11f−k** are indicated below.

(4*S*,5*S*,6*S*,1′*S*/*R*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-[acetyl(methoxycarbonyl)methyl]-tetrahydro-2-pyranone (11f) (as a mixture of epimers in the exocyclic position as well as a small amount of enol tautomer): $[\alpha]_D$ −18.2° (*c* = 0.7, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36−7.29 (m), 5.45 (q, *J* = 5.5, OH from the enol), 4.63−4.51 (m), 4.37−4.28 (m), 3.95−3.82 (m), 3.74 (m), 3.73 (s), 3.69 (s), 3.50 (d, *J* = 8.1), 3.20−3.07 (m), 2.83 (dd, *J* = 7.0, 17.5), 2.78 (dd, *J* = 6.8, 17.4), 2.42 (dd, *J* = 8.5, 17.5), 2.40 (dd, *J* = 7.6, 17.4), 2.19 (s), 2.16 (s), 1.42 (d, *J* = 5.5, CH_3 in the branched-chain in the enol tautomer), 0.893 (s), 0.886 (s), 0.08 (s), 0.07 (s); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 200.9 (s), 200.8 (s), 169.60 (s), 169.56 (s), 168.35 (s), 168.28 (s), 137.3 (s), 128.54 (d), 128.47 (d), 128.2 (d), 128.0 (d), 127.9 (d), 78.0 (d), 77.3 (d), 73.0 (d), 72.4 (t), 72.1 (d), 72.0 (t), 61.4 (d), 60.6 (d), 60.5 (t), 60.4 (t), 52.7 (q), 35.2 (d), 35.0 (d), 31.3 (t), 29.8 (q), 29.1 (q), 25.7 (q), 18.1 (s), 18.0 (s), 1.0 (q), −5.6 (q), −5.7 (q); MS *m*/*e* 407 (M-57, 0.1), 375 (0.5), 198 (3.6), 154 (5.3), 126 (12.9), 117 (4.1), 91 (100), 75 (6.2), 73 (7.6), 43 (8.6). Anal. Calcd for $C_{24}H_{36}O_7Si$: C, 62.04; H, 7.81. Found: C, 62.36; H, 8.08.

(4*S*,5*S*,6*S*,1′*R*/*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-[1-(ethoxycarbonyl)-2-oxocyclopentyl]-tetrahydro-2-pyranone (11g) (mixture of epimers in the exoheterocyclic carbon): $[\alpha]_D$ −35.2° (*c* = 0.42, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.31 (m, 10H), 4.56 (m, 4H), 4.41 (m, 2H), 4.31−4.08 (m, 5H), 4.02 (dd, *J* = 2.8, 5.0), 3.95 (dd, *J* = 2.6, 5.0), 3.92−3.86 (m, 3H), 3.03−1.89 (m, 18H), 1.23 (m, 6H), 0.91 (s, 9H), 0.89 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 212.9 (s), 212.6 (s), 170.6 (s), 170.5 (s), 169.4 (s), 137.6 (s), 137.5 (s), 128.3 (d), 127.8 (d), 127.7 (d), 127.6 (d), 127.5 (d), 78.8 (d), 78.3 (d), 73.4 (d), 72.7 (d), 72.2 (t), 71.6 (t), 62.61 (s,), 62.55 (s), 62.0 (t), 61.9 (t), 60.4 (t), 60.1 (t), 40.1 (d), 39.6 (d), 38.2 (t), 37.8 (t), 35.8 (t), 34.7 (t), 31.3 (t), 30.7 (t), 30.6 (t), 30.3 (t), 25.7 (q), 19.3 (s), 19.2 (s), 14.0 (q), −5.5 (q, $SiCH_3$), −5.6 (q); MS *m*/*e* 505 (M + 1, 0.06), 461 (0.12), 447 (0.4), 339 (0.4), 311 (0.4), 291 (2.6), 117 (3.4), 109 (2.8), 105 (24.7), 91 (100), 77 (5.0), 75 (7.0), 73 (7.6). Anal. Calcd for $C_{27}H_{40}O_7Si$: C, 64.26; H, 7.99. Found: C, 64.61; H, 8.18.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-[bis(methoxycarbonyl)methyl]tetrahydro-2-pyranone (11h): $[\alpha]_D$ −32.3° (*c* = 0.7, $CHCl_3$); ^{1}H-NMR (200 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.63 (d, *J* = 11.4, 1H), 4.55 (d, *J* = 11.5, 1H), 4.39−4.33 (m, 1H), 3.95−3.82 (m, 3H), 3.72 (s, 3H), 3.70 (s, 3H), 3.54 (d, *J* = 7.3, 1H), 3.13 (m, 1H), 2.85 (dd, *J* = 7.0, 17.4, 1H), 2.57 (dd, *J* = 8.5, 17.4, 1H), 0.89 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 169.6 (s), 168.0 (s), 167.9 (s), 137.2 (s), 128.5 (2C, d), 128.0 (d), 127.9 (2C, d), 77.5 (d), 72.4 (d), 72.2 (t), 60.3 (t), 52.7 (2C, q), 52.6 (d), 35.4 (d), 31.1 (t), 25.7 (3C, q), 18.1 (s), −5.6 (q), −5.7 (q); MS *m*/*e* 481 (M + 1, 0.01), 117 (11.1), 105 (4.0), 101 (4.3), 99 (5.9), 95 (4.4), 92 (41.2), 91 (100), 89 (14.7), 75 (17.9), 73 (21.8), 65 (13.1), 59 (17.0), 57 (11.9), 41 (9.8). Anal. Calcd for $C_{24}H_{36}O_8Si$: C, 59.97; H, 7.56. Found: C, 60.23; H, 7.32.

(4*S*,5*S*,6*S*)-5-(Benzyloxy)-6-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-[1,1-bis(ethoxycarbonyl)-3-butenyl]tetrahydro-2-pyranone (11i): $[\alpha]_D$ −20.3° (*c* = 0.9, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.76−5.64 (m, 1H), 5.16 (broad d, *J* = 6.8, 1H), 5.12 (broad s, 1 H), 4.76 (d, *J* = 11.7, 1H), 4.57 (d, *J* = 11.7, 1H), 4.30−4.14 (m, 5H), 4.11 (distorted t, *J* = 2.3, 1H), 3.83 (d, *J* = 6.6, 2H), 2.93 (distorted td, *J* = 2.8, 8.1, 1H), 2.78 (dd, *J* = 7.6, 16.4, 1H), 2.67 (broad d, *J* = 7.3, 1H), 2.58 (dd, *J* = 8.9, 16.4, 1H), 1.27 (t, *J* = 7.2, 3H), 1.26 (t, *J* = 7.1, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 170.6 (s), 170.0 (s), 169.5 (s), 138.0 (s), 131.9 (d), 128.3 (2C), 127.6 (d), 127.4 (2C, d), 119.7 (t), 78.9 (d), 72.2 (d), 71.9 (t), 61.7 (2C, t), 60.9 (t), 59.4 (s), 40.0 (d), 38.0 (t), 30.1 (t), 25.8 (3C, q), 18.1 (s), 14.0 (q), 13.9 (q), −5.5 (q), −5.6 (q); MS *m*/*e* 491 (M − 57, 0.3), 385 (0.4), 291 (2.4), 117 (3.2), 91 (100), 75 (5.4), 73 (8.0), 69 (6.9). Anal. Calcd for $C_{29}H_{44}O_8Si$: C, 63.47; H, 8.09. Found: C, 63.75; H, 7.92.

(4*S*,5*S*,6*S*,1′*R*/*S*)-5-[[(Benzyloxy)-6-(*tert*-butyldimethylsilyl)oxy]methyl]-4-[(diphenylmethyleneamino)(methoxycarbonyl)methyl]tetrahydro-2-pyranone (11k) (mixture of epimers in the exocyclic carbon): $[\alpha]_D$ −48.1 (*c* = 1.0, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.65−7.61 (m, 4H), 7.48−7.26 (m, 20H), 7.20−7.11 (m, 4H), 7.08−7.04 (m, 2H), 4.67 (d, *J* = 11.7, 1H), 4.52 (d, *J* = 11.8, 1H), 4.51 (m, 1H), 4.50 (d, *J* = 11.7, 1H), 4.44 (d, *J* = 11.8, 1H), 4.33 (distorted ddd, *J* = 2.7, 4.4, 6.9, 1H), 4.26 (d, *J* = 2.4, 1H), 4.24 (dd, *J* = 2.6, 4.0, 1H), 4.08 (d, *J* = 4.6, 1H), 3.93−3.84 (m, 4H), 3,73 (m, 1H), 3.67 (s, 3H), 3.64 (s, 3H), 3.19 (dd, *J* = 8.9, 16.3, 1H), 3.04 (m, 2H), 2.69 (dd, *J* = 6.8, 16.3, 1H), 2.65 (dd, *J* = 7.1, 16.5, 1H), 2.29 (dd, *J* = 8.5, 16.5, 1H), 0.88 (s, 9H), 0.80 (s, 9H), 0.09 (s, 3H), 0.06 (s, 3H), 0.00 (s, 3H), −0.03 (s, 3H); ^{13}C-NMR (50.3 MHz, $CDCl_3$) δ 173.1 (s), 17.8 (s), 171.3 (s), 171.0 (s), 170.8 (s),138.7 (s), 138.6 (s), 137.8 (s), 137.5 (s), 136.0 (s), 135.7 (s), 131.0 (d), 130.9 (d), 129.0 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.4 (d), 128.3 (d), 128.2 (d), 127.8 (d), 127.7 (d), 127.45 (d), 127.35 (d), 127.3 (d), 79.4 (d), 78.4 (d), 73.0 (d), 71.8 (d), 71.6 (t), 66.2 (d), 65.2 (d), 60.9 (t), 60.3 (t), 52.3 (q), 52.2 (q), 39.5 (d), 39.2 (d), 31.2 (t), 29.5 (t), 25.8 (3C, q), 25.7 (3C, q), 18.14 (s), 18.06 (s), −5.5 (q), −5.6 (q), −5.7 (q); MS *m*/*e* 605 (0.5), 604 (2.1), 603 (6.6), 602 (18.9, M+1), 600 (0.6), 544 (13.2), 510 (2.5), 495 (2.3), 494 (5.3), 253 (5.0), 252 (9.7), 193 (13.8), 91 (100). Anal. Calcd for $C_{35}H_{43}NO_6Si$: C, 69.85; H, 7.21; N, 2.33. Found: C, 69.48; H, 7.42; N, 2.37.

Acknowledgment. Financial support from DGICYT (Project numbers PB-93-0154 and PB-94-0104) is gratefully acknowledged. We also thank the CSIC-CNR exchange program and the Spanish Ministry of Education of Education (grant to R.B.) for additional support.

JO9514836