JOC Note
pubs.acs.org/joc

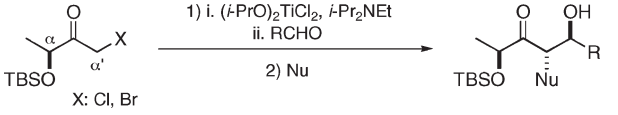
Stereoselective Synthesis of Highly Functionalized Structures from Lactate-Derived Halo Ketones†

Joaquim Nebot, Pedro Romea,* and Fèlix Urpí*

Departament de Química Orgànica, Universitat de Barcelona, Martí i Franqués 1-11, 08028 Barcelona, Catalonia, Spain

felix.urpi@ub.edu; pedro.romea@ub.edu

Received June 3, 2009



Highly diastereoselective $(i\text{-PrO})_2TiCl_2$-mediated aldol reactions from lactate-derived α′-halo α-silyloxy ketones and subsequent treatment of the resultant aldols with a wide range of nucleophiles furnishes highly functionalized arrangements useful in natural product syntheses.

The stereoselective aldol reaction based on substrates containing a heteroatom at the enolizable position constitutes a powerful tool for the construction of complex arrangements of functionality and stereochemistry in natural product syntheses.[1] Indeed, the *glycolate* aldol reactions of hydroxy ketones,[2,3] esters,[4] thioesters,[5] and imides[6] have been widely used for the synthesis of polyoxygenated structures, whereas related aminooxygenated arrays have been obtained from isothiocyanateacetyl oxazolidinones[7] and, more recently, an azidoacetyl thiazolidinethione.[8] In turn, similar halo carboxylic systems have been also engaged in such kinds of reactions,[5a,9] but few methodologies have taken advantage of the synthetic potentiality of chiral halo ketones.[10,11] Thus, considering the ability of halides as leaving groups in S_N2-like processes and the high diastereoselectivity achieved by the aldol reactions of chiral α-hydroxy ketones,[12] we envisaged that parallel substrate-controlled additions from α′-halo α-silyloxy ketones would afford the *syn-syn* halo aldols, which might be subsequently transformed into highly functionalized molecular architectures (see Scheme 1). Herein we disclose the success of such a strategy based on the titanium-mediated aldol reactions of lactate-derived α′-chloro- and α′-bromo-α-*tert*-butyldimethylsilyloxy ketones (R^1: Me; R_3Si: TBS; X: Cl, Br in Scheme 1).[13]

The required chloro and bromo ketones (**1** and **2**, respectively, see Table 1) were prepared from commercially available ethyl lactate following procedures reported in the literature.[14] With a straightforward and reliable supply of ketones **1** and **2** in hand, we began to study their titanium-mediated aldol reactions. Preliminary studies with $TiCl_4$ and isobutyraldehyde (**a**) were disappointing. The experimental

† This paper is dedicated to Prof. Santiago Olivella on the occasion of his 65th birthday.

(1) For an overview on aldol methodologies for the synthesis of polyketides, see: Schetter, B.; Mahrwald, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 7506.

(2) (a) Paterson, I.; Tillyer, R. D. *J. Org. Chem.* **1993**, *58*, 4182. (b) Hayward, C. M.; Yohannes, D.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1993**, *115*, 9345. (c) Paterson, I.; Doughty, V. A.; McLeod, M. D.; Trieselmann, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1308. (d) Trost, B. M.; Ito, H.; Silcoff, E. R. *J. Am. Chem. Soc.* **2001**, *123*, 3367. (e) Murga, J.; Ruiz, P.; Falomir, E.; Carda, M.; Peris, G.; Marco, J. A. *J. Org. Chem.* **2004**, *69*, 1987. (f) Evans, D. A.; Glorius, F.; Burch, J. D. *Org. Lett.* **2005**, *7*, 3331.

(3) For a review on aldol additions of dihydroxyacetone, see: Markert, M.; Mahrwald, R. *Chem. Eur. J.* **2008**, *14*, 40.

(4) (a) Andrus, M. B.; Soma Sekhar, B. B. V.; Meredith, E. L.; Dalley, N. K. *Org. Lett.* **2000**, *2*, 3035. (b) Dixon, D. J.; Ley, S. V.; Polara, A.; Sheppard, T. *Org. Lett.* **2001**, *3*, 3479. (c) Andrus, M. B.; Soma Sekhar, B. B. V.; Turner, T. M.; Meredith, E. L. *Tetrahedron Lett.* **2001**, *42*, 7197. (d) Denmark, S. E.; Chung, W.-j. *J. Org. Chem.* **2008**, *73*, 4582.

(5) (a) Gennari, C.; Vulpetti, A.; Pain, G. *Tetrahedron* **1997**, *53*, 5909. (b) Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472. (c) Fanjul, S.; Hulme, A. N. *J. Org. Chem.* **2008**, *73*, 9788.

(6) For representative examples, see: (a) Evans, D. A.; Gage, J. R.; Leighton, J. L; Kim, A. S. *J. Org. Chem.* **1992**, *57*, 1961. (b) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001. (c) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (d) Li, Z.; Wu, R.; Michalczyk, R.; Dunlap, R. B.; Odom, J. D.; Silks, L. A. *J. Am. Chem. Soc.* **2000**, *122*, 386. (e) Crimmins, M. T.; McDougall, P. J. *Org. Lett.* **2003**, *5*, 591. (f) Zhang, W.; Carter, R. G.; Yokochi, A. F. T. *J. Org. Chem.* **2004**, *69*, 2569. (g) Owen, R. M.; Roush, W. R. *Org. Lett.* **2005**, *7*, 3941. (h) Vincent, G.; Mansfield, D. J.; Vors, J.-P.; Ciufolini, M. A. *Org. Lett.* **2006**, *8*, 2791. (i) Crimmins, M. T.; Ellis, J. M. *J. Org. Chem.* **2008**, *73*, 1649.

(7) For representative examples, see: (a) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1986**, *108*, 6757. (b) Boger, D. L.; Colletti, S. L.; Honda, T.; Menezes, R. F. *J. Am. Chem. Soc.* **1994**, *116*, 5607. (c) Herbert, B.; Kim, I. H.; Kirk, K. L. *J. Org. Chem.* **2001**, *66*, 4892. (d) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1543.

(8) Patel, J.; Clavé, G.; Renard, P.-Y.; Franck, X. *Angew. Chem., Int. Ed.* **2008**, *47*, 4224.

(9) (a) Abdel-Magid, A.; Pridgen, L. N.; Eggleston, D. S.; Lantos, I. *J. Am. Chem. Soc.* **1986**, *108*, 4595. (b) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (c) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (d) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998. (e) Wang, Y.-C.; Su, D.-W.; Lin, C.-W.; Tseng, H.-L.; Li, C.-L.; Yan, T.-H. *J. Org. Chem.* **1999**, *64*, 6495. (f) Ghosh, A. K.; Kim, J.-H. *Org. Lett.* **2004**, *6*, 2725. (g) Hoover, T. R.; Groeper, J. A.; Parrott, R. W.; Chandrashekar, S. P.; Finefield, J. M.; Dominguez, A.; Hitchcock, S. R. *Tetrahedron: Asymmetry* **2006**, *17*, 1831. (h) Son, J. B.; Hwang, M.-h.; Lee, W.; Lee, D.-H. *Org. Lett.* **2007**, *9*, 3897. (i) Yu, D.-S.; Xu, W.-X.; Liu, L.-X.; Huang, P.-Q. *Synlett* **2008**, 1189.

(10) (a) Enders, D.; Hett, R. *Synlett* **1998**, 961. (b) Palomo, C.; Oiarbide, M.; Sharma, A. K.; González-Rego, M. C.; Linden, A.; García, J. M.; González, A. *J. Org. Chem.* **2000**, *65*, 9007.

(11) For organocatalyzed reactions from chloroacetone, see: (a) He, L.; Tang, Z.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron* **2006**, *62*, 346. (b) Guillena, G.; Hita, M. C.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 1272.

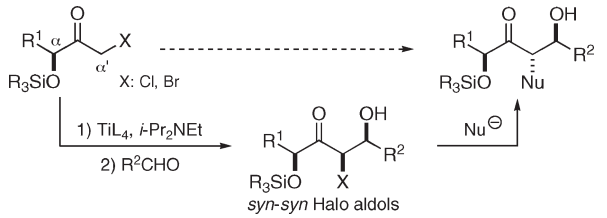
(12) For seminal contributions on stereoselective aldol reactions based on chiral α-hydroxy ketones, see: (a) Masamune, S.; Choy, W.; Kerdesky, F. A. J.; Imperiali, B. *J. Am. Chem. Soc.* **1981**, *103*, 1566. (b) Van Draanen, N. A.; Arseniyadis, S.; Crimmins, M. T.; Heathcock, C. H. *J. Org. Chem.* **1991**, *56*, 2499. (c) Paterson, I.; Wallace, D. J.; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *33*, 9083.

(13) For titanium-mediated aldol reactions from lactate-derived ethyl and methyl ketones, see: (a) Solsona, J. G.; Romea, P.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2003**, *5*, 519. (b) Solsona, J. G.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2004**, *45*, 5379. (c) Nebot, J.; Figueras, S.; Romea, P.; Urpí, F.; Ji, Y. *Tetrahedron* **2006**, *62*, 11090. (d) Rodríguez-Cisterna, V.; Villar, C.; Romea, P.; Urpí, F. *J. Org. Chem.* **2007**, *72*, 6631. (e) Pellicena, M.; Solsona, J. G.; Romea, P.; Urpí, F. *Tetrahedron Lett.* **2008**, *49*, 5265.

(14) (a) Barluenga, J.; Baragaña, B.; Alonso, A.; Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 969. (b) Kaluza, Z.; Kazimierski, A.; Lewandowski, K.; Suwinska, K.; Szczesna, B.; Chmielewski, M. *Tetrahedron* **2003**, *59*, 5893.

Published on Web 09/04/2009 DOI: 10.1021/jo9010798

SCHEME 1



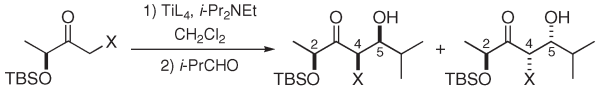
conditions early used for the structurally related ethyl ketone (method A: (i) TiL_n, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 30 min; (ii) *i*-PrCHO, −78 °C, 30 min) afforded the 2,4-*syn*-4,5-*syn* halo aldols **4a** (X: Cl) and **6a** (X: Br) in high yields but in lower diastereomeric ratios than expected (see entries 1 and 2 in Table 1).[15,16] Therefore, other titanium(IV) Lewis acids were surveyed. We were pleased to observe that the diastereoselectivity could be improved using weaker Lewis acids as (*i*-PrO)$TiCl_3$ or (*i*-PrO)$_2TiCl_2$ (compare entries 1−6 in Table 1). Such improvement was particularly remarkable with (*i*-PrO)$_2TiCl_2$, although **4a** and **6a** were isolated in low yields (see entries 5 and 6 in Table 1). Given that these discouraging results could be due to an incomplete enolization or to the lack of reactivity of the resultant titanium enolate, we carried out an exhaustive optimization of the temperature and the reaction time both on the enolization and the aldol addition steps. Finally, we found a new set of conditions (method B: (i) (*i*-PrO)$_2TiCl_2$, *i*-Pr_2NEt, CH_2Cl_2, −78 to −20 °C, 1.5 h; (ii) *i*-PrCHO, −78 °C for 2 h, −20 °C for 1 h) that provide **4a** and **6a** in good yields and excellent diastereomeric ratios (see entries 7 and 8 in Table 1).

Having established the best experimental conditions for isobutyraldehyde, we next surveyed a wide range of aldehydes to determine the scope of the reaction. The results are summarized in Table 2. As shown, both ketones delivered the corresponding 2,4-*syn*-4,5-*syn* halo aldols in good yields (67−78%) and high diastereomeric ratios (dr > 92:8). Particularly outstanding were the results of bromo ketone **2** with aliphatic and α,β-unsaturated aldehydes (see entries 4−6, 8, and 9 in Table 2) since a single aldol **6** was identified in the reaction mixtures irrespective of the steric hindrance.

Although a thorough understanding of the stereochemical outcome of these reactions is hampered by the lack of knowledge on the structure of the titanium enolates,[17] it is likely that they involve a *Z*-enolate that evolves through a cyclic six-membered chairlike transition state. Then, the antiperiplanar distribution of TBSO−C and C−OTi bonds shapes the configuration of the major aldol **4** or **6** since the less sterically demanding Cα substituent (H vs Me) is placed pointing toward the inside of the ring (Scheme 2).[12]

We are aware that this model does not easily account for the influence of the halide and the substituents of the titanium on the diastereoselectivity. Regarding the impact of the halides, it might be tentatively traced to steric effects. Indeed, a bare inspection of the results represented in Figure 1 for the titanium-mediated aldol reactions of several

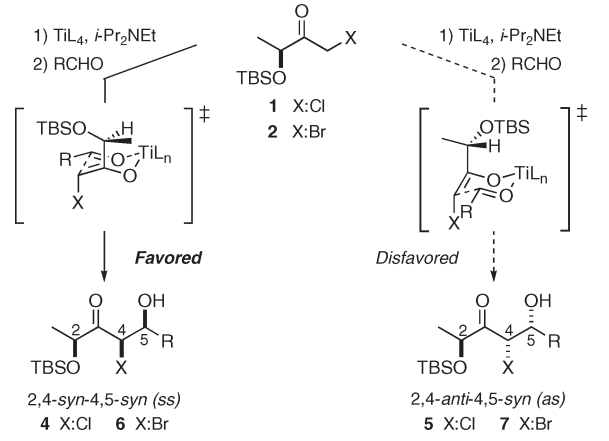
TABLE 1. Titanium-Mediated Aldol Reactions of Lactate-Derived Ketones 1 and 2 with Isobutyraldehyde (a)



entry	ketone	TiL_4	aldol	dr (*ss*/*as*)[a]	yield[b] (%)
1[c]	**1**	$TiCl_4$	**4a**	82:18	79
2[c]	**2**	$TiCl_4$	**6a**	90:10	81
3[c]	**1**	(*i*-PrO)$TiCl_3$	**4a**	91:9	77
4[c]	**2**	(*i*-PrO)$TiCl_3$	**6a**	94:6	79
5[c]	**1**	(*i*-PrO)$_2TiCl_2$	**4a**	97:3	40
6[c]	**2**	(*i*-PrO)$_2TiCl_2$	**6a**	> 97:3	35
7[d]	**1**	(*i*-PrO)$_2TiCl_2$	**4a**	97:3	74
8[d]	**2**	(*i*-PrO)$_2TiCl_2$	**6a**	> 97:3	69

[a]Determined by ^1H NMR analysis of the reaction mixture. [b]Overall isolated yield. [c]Method A: (i) TiL_4, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 30 min; (ii) *i*-PrCHO, −78 °C, 30 min. [d]Method B: (i) TiL_4, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 15 min, −20 °C, 1.5 h; (ii) *i*-PrCHO, −78 °C, 2 h, −20 °C, 1 h.

SCHEME 2. Mechanistic Model for Aldol Reactions from 1 and 2



lactate-derived silyloxy ketones with isobutyraldehyde shows that the smaller the X group the worse the diastereoselectivity. However, the diastereoselectivity of the ethyl (X: Me)[13c] and methyl ketones (X: H)[18] is rather insensitive to the titanium Lewis acid, which suggests that not steric but other electronic effects may be the reasons for the changes in the diastereoselectivity observed across the whole series.[19]

The remarkable stereocontrol on the aldol reactions from bromo ketone **2** and the apparent ease of displacement of bromine in S_N2-like processes made aldols **6** highly appealing substrates to undertake their conversion into highly functionalized structures. Initially, we assessed the intermolecular substitution of the bromine with a large set of oxygenated nucleophiles including carboxylates, alcohols, and water. To our displeasure and in spite of many efforts, we were unable to obtain the fully oxygenated system.

(15) For the proof of the stereochemsitry of **4a** and **6a**, see the Supporting Information.

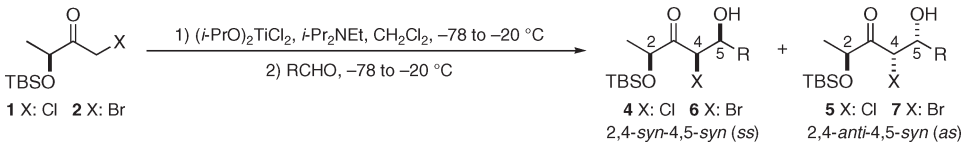
(16) The halo aldols 2,4-*syn*-4,5-*syn* (**4a** or **6a**) and 2,4-*anti*-4,5-*syn* (**5a** or **7a**) were the only diastereomers observed in the reaction mixtures.

(17) For the biradical character of some titanium(IV) enolates, see: Moreira, I.; de, P. R.; Bofill, J. M.; Anglada, J. M.; Solsona, J. G.; Nebot, J.; Romea, P.; Urpí, F. *J. Am. Chem. Soc.* **2008**, *130*, 3242.

(18) Unpublished results from Lorente, A. Màster Experimental, Universitat de Barcelona, 2009.

(19) The influence of Ti−Lewis acids on the aldol reactions of *tert*-butyl hydroxyacetate has been reported; see: Gawas, D.; Kazmaier, U. *J. Org. Chem.* **2009**, *74*, 1788.

TABLE 2. $(i\text{-PrO})_2TiCl_2$-Mediated Aldol Reactions of Lactate-Derived Ketones 1 and 2



entry	ketone	aldehyde	R	aldol	dr (*ss*/*as*)[a]	yield[b] (%)
1	**1**	**a**	*i*-Pr	**4a**	97:3	74
2	**1**	**d**	Ph	**4d**	94:6	67
3	**1**	**e**	(*E*) CH=CHCH$_3$	**4e**	97:3	71
4	**2**	**a**	*i*-Pr	**6a**	>97:3	69
5	**2**	**b**	*i*-Bu	**6b**	>97:3	70
6	**2**	**c**	Et	**6c**	>97:3	77
7	**2**	**d**	Ph	**6d**	92:8	70
8	**2**	**e**	(*E*) CH=CHCH$_3$	**6e**	>97:3	78
9	**2**	**f**	C(CH$_3$)=CH$_2$	**6f**	95:5	70

[a]Determined by ^{1}H NMR analysis of the reaction mixture. [b]Overall isolated yield.

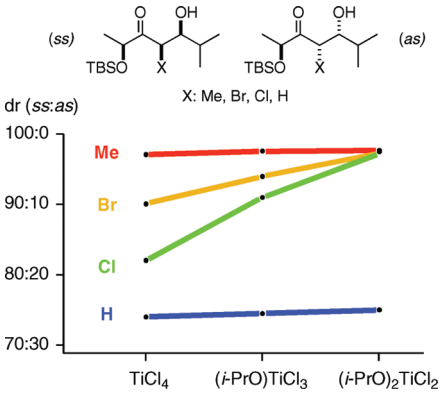


FIGURE 1. Diastereoselectivity of titanium-mediated aldol reactions from lactate-derived ketones.

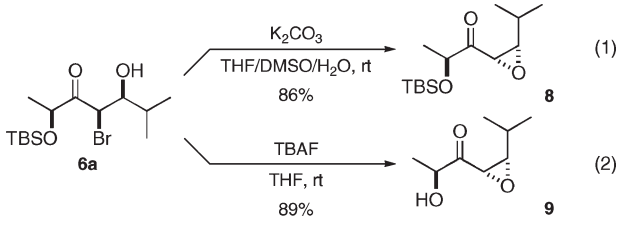
Instead, we took advantage of the vicinal alcohol and triggered the intramolecular cyclization to prepare *cis*-α, *β*-epoxy ketones **8** and **9** in high yields by treatment of **6a** with K_2CO_3 or TBAF (see eqs 1 and 2 in Scheme 3).

The introduction of a nitrogenated nucleophile became a thorny transformation as well. Indeed, the intermolecular reaction required a careful optimization to avoid undesired epimerizations, but we finally found that the reaction of **6a** with NaN_3 in DMSO furnished the azido derivative **10** in 84% yield (see eq 3 in Scheme 4). Once the intermolecular process had been completed, we next examined the intramolecular counterpart. Thus, we were pleased to observe that treatment of **6a** with *N*-tosylisocyanate produced a carbamate, which afforded the oxazolidinone **11** upon addition of K_2CO_3 (see eq 4 in Scheme 4).

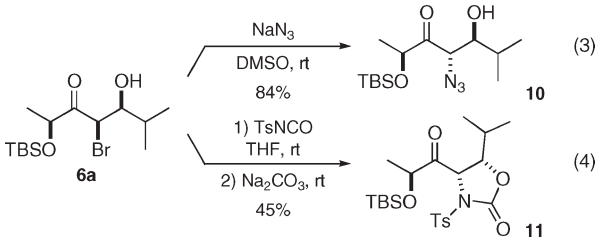
Eventually, we took advantage of the reactivity of sulfur nucleophiles. Therefore, a thiophenol group was introduced on TES-protected bromo aldol **12** in the presence of K_2CO_3 (see eq 5 in Scheme 5), whereas the thioacetate did not require any protection and enabled the ready transformation of **6e** into **14** in excellent yield (see eq 6 in Scheme 5).

In summary, we have developed a new substrate-controlled aldol reaction from lactate-derived α′-halo α-silyloxy ketones. It is noteworthy, the titanium Lewis acid used for the enolization of these ketones plays a crucial role on the diastereoselectivity of the reaction, having established that

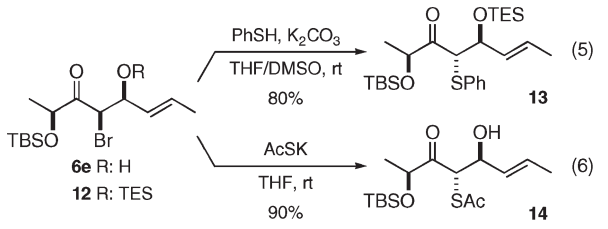
SCHEME 3



SCHEME 4



SCHEME 5



the weak Lewis acid $(i\text{-PrO})_2TiCl_2$ must be employed to achieve diastereomeric ratios up to 97:3 of the corresponding 2,4-*syn*-4,5-*syn* halo aldols. Furthermore, the resultant bromo aldols have been converted into complex arrangements of functionality and stereochemistry through S_N2-like inter- and intramolecular transformations.

Experimental Section

General Procedure for the Titanium-Mediated Aldol Reactions from 1 and 2. Recently distilled $(i\text{-PrO})_4Ti$ (163 μL, 0.55 mmol) was added to a solution of $TiCl_4$ (60 μL, 0.55 mmol) in CH_2Cl_2 (1 mL) at 0 °C under N_2. The resultant mixture was stirred for

10 min at 0 °C, diluted with CH_2Cl_2 (1 mL), and further stirred for 10 min at room temperature, which afforded an almost colorless solution. This $(i\text{-PrO})_2TiCl_2$ (1.1 mmol) solution in CH_2Cl_2 (2 mL) was carefully added via cannula (+1 mL of CH_2Cl_2) to a solution of **1** or **2** (1 mmol) in CH_2Cl_2 (2 mL) at −78 °C under N_2, which developed a yellow-orange color. It was stirred for 3−4 min at −78 °C, and *i*-Pr_2NEt (190 μL, 1.1 mmol) was dropwise added. The resultant mixture was stirred for 15 min at −78 °C and 1.5 h at −20 °C. Eventually, the color of the reaction mixture became dark red. Then, it was cooled at −78 °C, and a recently distilled aldehyde (1.5 mmol) was added. The mixture was stirred for 2 h at −78 °C and 1 h at −20 °C. The reaction was quenched by addition of satd NH_4Cl (5 mL). The mixture was diluted with Et_2O and washed with H_2O, satd $NaHCO_3$, and brine, and the aqueous layers were extracted with Et_2O. The organic extracts were dried and concentrated. The residue was analyzed by ^1H NMR and purified by column chromatography to afford the desired aldols **4** or **6**. **Note:** Aldols **6** must be handled with care. They must be concentrated at room temperature, kept in the refrigerator (−20 °C), and used within weeks.

6a: R_f (hexanes/EtOAc 90:10) = 0.25; $[\alpha]^{20}_D$ +68.7 (*c* 1.1, $CHCl_3$); IR (film) ν 3529, 2960, 2860, 1717, 1472 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ5.06 (1H, d, J = 3.1 Hz), 4.34 (1H, q, J = 6.8 Hz), 3.43 (1H, dt, J = 7.8 Hz, J = 3.1 Hz), 3.31 (1H, d, J = 3.1 Hz), 1.91−1.79 (1H, m), 1.51 (3H, d, J = 6.8 Hz), 1.05 (3H, d, J = 6.6 Hz), 0.93 (9H, s), 0.91 (3H, d, J = 6.8 Hz), 0.12 (3H, s), 0.09 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 208.9, 75.0, 73.9, 48.6, 31.6, 25.7, 22.9, 18.8, 18.3, 18.0, −4.5, −5.0; HRMS (+ESI) *m*/*z* calcd for $C_{14}H_{30}{}^{79}BrO_3Si$ $[M + H]^+$ 353.1142, found 3053.1139.

Preparation of (2*S*,4*S*,5*S*)-2-(*tert*-Butyldimethylsilyloxy)-4,5-epoxy-6-methyl-3-heptanone (8). A mixture of **6a** (87 mg, 0.25 mmol) and K_2CO_3 (171 mg, 1.24 mmol) in 50:10:1 THF/DMSO/H_2O (2.4 mL) was stirred for 3 h at room temperature under N_2. The reaction mixture was partitioned in 1:1 Et_2O/H_2O (50 mL), and the aqueous layer was extracted with Et_2O (15 mL). The organic extracts were dried and concentrated. The resultant oil was purified through column chromatography (hexanes/EtOAc 90:10) to afford 58 mg (86% yield) of **8** as a colorless oil: R_f (hexanes/EtOAc 90:10) = 0.35; $[\alpha]^{20}_D$ −55.1 (*c* 0.65, $CHCl_3$); IR (film) ν 2961, 2859, 1729, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ4.37 (1H, q, J = 6.7 Hz), 4.09 (1H, d, J = 4.9 Hz), 2.97 (1H, dd, J = 9.4 Hz, J = 4.9 Hz), 1.43−1.33 (1H, m), 1.32 (3H, d, J = 6.7 Hz), 1.11 (d, J = 6.6 Hz), 0.93 (9H, s), 0.91 (d, J = 6.8 Hz), 0.14 (3H, s), 0.13 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 207.4, 74.4, 65.1, 57.8, 26.2, 25.6, 20.0, 19.9, 18.4, 17.9, −4.5, −5.2; HRMS (+FAB) *m*/*z* calcd for $C_{14}H_{29}O_3Si$ $[M + H]^+$ 273.1886, found 273.1898.

Preparation of (2*S*,4*S*,5*S*)-4-Azido-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-6-methyl-3-heptanone (10). A mixture of **6a** (50 mg, 141 μmol) and NaN_3 (9.7 mg, 149 μmol) in DMSO (0.5 mL) was stirred at room temperature for 2 h under N_2. The reaction mixture was diluted with Et_2O and washed with H_2O and brine. The aqueous layers were extracted with Et_2O, and the organic extracts were dried and concentrated. The resultant oil was purified by column chromatography (hexanes/EtOAc 80:20) to afford 37.5 mg (84% yield) of **10** as a colorless oil: R_f (hexanes/EtOAc 80:20) = 0.50; $[\alpha]^{20}_D$ +84.7 (*c* 1.1, $CHCl_3$); IR (film) ν 3503, 2960, 2860, 2103, 1725, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ4.36 (1H, q, J = 6.8 Hz), 4.23 (1H, d, J = 8.6 Hz), 3.78 (1H, ddd, J = 8.6 Hz, J = 7.4 Hz, J = 3.7 Hz), 2.49 (1H, d, J = 7.4 Hz), 2.01−1.90 (1H, m), 1.38 (3H, d, J = 6.8 Hz), 1.03 (3H, d, J = 6.9 Hz), 0.96 (3H, J = 6.8 Hz), 0.93 (9H, s), 0.15 (3H, s), 0.13 (3H, s); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 210.3, 75.6, 74.4, 60.9, 30.5, 25.8, 19.9, 19.4, 18.1, 15.3, −4.8, −4.8; HRMS (+FAB) *m*/*z* calcd for $C_{14}H_{30}N_3O_3Si$ $[M + H]^+$ 316.2050, found 316.2050.

Preparation of *S*-[(2*S*,4*S*,5*S*,6*E*)-2-(*tert*-butyldimethylsilyloxy)-5-hydroxy-3-oxo-6-octen-4-yl] Thioacetate (14). A mixture of **6e** (36 mg, 102 μmol) and AcSK (12.3 mg, 108 μmol) in 40:8:1 THF/DMSO/H_2O (1 mL) was stirred for 20 min at room temperature under N_2. The reaction mixture was partitioned with 1:1 CH_2Cl_2/pH 7 phosphate buffer, and the aqueous layer was extracted with CH_2Cl_2. The organic extracts were dried and concentrated. The resultant oil was purified through column chromatography (hexanes/EtOAc 85:15) to afford 32 mg (90% yield) of **14** as a colorless oil: R_f (hexanes/EtOAc 85:15) = 0.25; $[\alpha]^{20}_D$ −65.2 (*c* 0.5, $CHCl_3$); IR (film) ν 3475, 2930, 2857, 1702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (1H, dqd, J = 15.2 Hz, J = 6.5 Hz, J = 1.0 Hz), 5.45 (1H, ddq, J = 15.2 Hz, J = 6.9 Hz, J = 1.6 Hz), 4.93 (1H, d, J = 7.1 Hz), 4.36 (1H, q, J = 6.8 Hz), 4.36−4.28 (1H, m), 3.02 (1H, d, J = 7.6 Hz), 2.32 (3H, s), 1.69 (3H, ddd, J = 6.5 Hz, J = 1.6 Hz, J = 1.0 Hz), 1.33 (3H, d, J = 6.8 Hz), 0.94 (9H, s), 0.16 (3H, s), 0.13 (3H, s); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 209.7, 193.8, 130.1, 129.6, 74.5, 73.3, 51.4, 30.1, 25.7, 19.7, 18.0, 17.6, −4.7, −4.9; HRMS (+ESI) *m*/*z* calcd for $C_{16}H_{30}NaO_4SSi$ $[M + Na]^+$ 369.1526, found 369.1511.

Acknowledgment. Financial support from the Spanish Ministerio de Ciencia y Tecnología and Fondos FEDER (Grant No. CTQ2006-13249/BQU) and the Generalitat de Catalunya (2005SGR00584), as well as a doctorate studentship to J.N. (Universitat de Barcelona), are acknowledged.

Supporting Information Available: Experimental procedures, physical and spectroscopic data for ketones **1** and **2**, aldols **4** and **6**, and derivatives **8**−**11**, **13**, and **14** and proof of stereochemistry of **4a** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.