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Michael Addition–Elimination Reactions of Chiral Enolates with Ethyl 3-Halopropenoates

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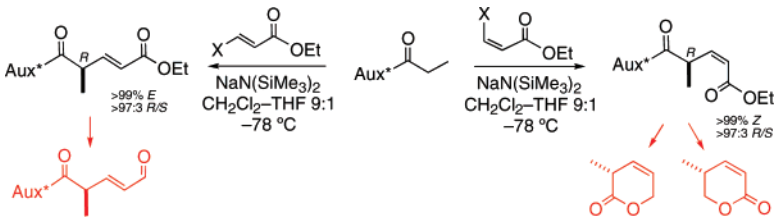
ABSTRACT

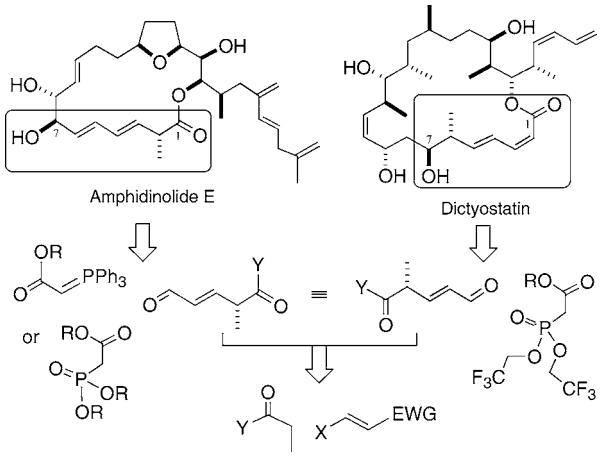


Key dienoic or dienal substructures of cytotoxic macrolides amphidinolide E and dictyostatin have been prepared via a Michael addition (followed by elimination of X^-) of chiral enolates on β-halo derivatives of ethyl acrylate, with full retention of the initial *E* or *Z* configuration. Evans oxazolidin-2-ones and our related thiazolidin-2-ones, as well as a fine-tuning of the reaction conditions, have been essential. Many chiral building blocks are accessible from these adducts.

In connection with a total synthesis of amphidinolide E,[1] we analyzed several strategies to reach the fragment tagged in Scheme 1 (C1−C7).[1e] Similar moieties are found in other interesting molecules, such as in the microtubule-stabilizing anticancer agent dictyostatin (fragment C1−C7).[2] These and related fragments can be prepared by a suitable manipulation of methyl (*R*)-3-hydroxy-2-methylpropanoate (the Roche ester) or by a Pd-catalyzed cross-coupling of appropriate synthons, but our interest in asymmetric Michael reactions[3] prompted us to evaluate also the disconnections shown in Scheme 1.

Michael additions of Ti enolates from chiral propanoyl derivatives (Aux*COEt) to activated double bonds (such as

Scheme 1. Dienal and/or Dienoate Fragments of Amphidinolide E and Dictyostatin



$H_2C{=}CH{-}COOMe$), to afford 1,5-difunctional synthons of type **1**, have been reported;[4] it is known that alkaline metal enolates do not undergo such a reaction (Scheme 2).[3,4] Conversion of C-trisubstituted enolates to compounds with

(1) Structure: (a) Kubota, T.; Tsuda, M.; Kobayashi, J. *J. Org. Chem.* **2002**, *67*, 1651. Total syntheses: (b) Va, P.; Roush, W. R. *J. Am. Chem. Soc.* **2006**, *128*, 15960. (c) Kim, C. H.; An, H. J.; Shin, W. K.; Yu, W.; Woo, S. K.; Jung, S. K.; Lee, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 8019. (d) Va, P.; Roush, W. R. *Tetrahedron* **2007**, *63*, 5768 and references therein. (e) Esteban, J. Ph.D. unpublished results.

(2) Reviews on total syntheses of dictyostatin (and other marine macrolides): (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237. (b) Nicholas, G. M.; Phillips, A. J. *Nat. Prod. Rep.* **2006**, *23*, 79. (c) Morris, J. C.; Nicholas, G. M.; Phillips, J. *Nat. Prod. Rep.* **2007**, *24*, 87.

(3) For example: (a) Mas, G.; González, L.; Vilarrasa, J. *Tetrahedron Lett.* **2003**, *44*, 8805. (b) Rodríguez-Escrich, C.; Olivella, A.; Urpí, F.; Vilarrasa, J. *Org. Lett.* **2007**, *9*, 989.

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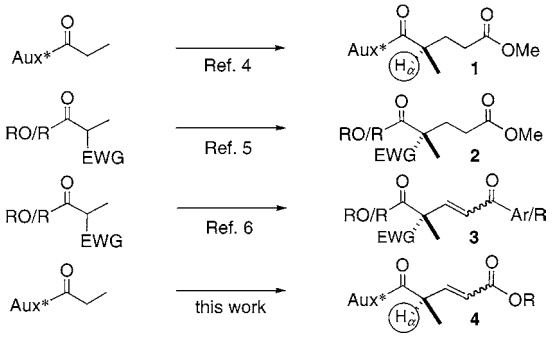
Scheme 2. Alkylation of Enolates via Michael Reactions

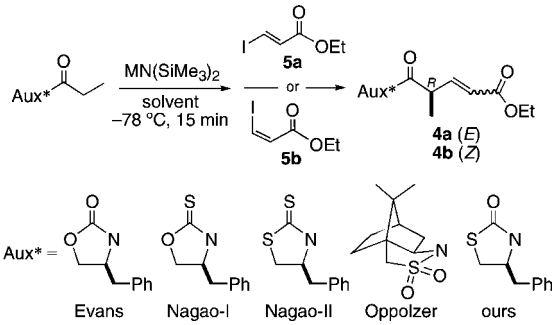


quaternary carbons (e.g., **2** and **3**), often in the presence of chiral phase-transfer catalysts (PTC), has also been developed.[5,6] While molecules of type **2** and **3** cannot epimerize, our challenge was to obtain structures of type **4**, which can show a higher tendency to epimerize than **1** due to the higher acidity of H_α (as the deprotonation of **4** gives rise to a very delocalized enolate); control of the double bond configuration was also essential. Thus, proton exchanges between **4** and the base excess or between **4** and the enolate had to be reduced to a minimum; in principle, catalytic processes and heating seemed counter-indicated.

We report here how we obtained enantiopure compounds of type **4** in excellent yields by using haloacrylates (e.g., **5a** and **5b**). The resulting products could be easily converted to a plethora of C1−C5 chiral fragments.

We carried out the first trial experiments with B, Ti, and Li enolates of the Evans most common auxiliary[7] and the ethyl ester of (*E*)-3-iodopropenoic acid (iodoacrylate **5a**). No reaction occurred in the first two cases, in CH_2Cl_2, even at room temperature (rt). With the Li enolate and **5b** in THF at −78 °C, the reaction was too slow, while at −40 °C for several hours, 40−60% of conversion was observed, but unfortunately, we obtained a mixture of diastereomers (the diastereomeric ratios, dr, were ca. 85:15 *R/S* and 20:80 *E/Z*). This outcome was not useful but indicated that a suitable optimization could provide the desired results. Table 1 summarizes the most significant results among more than 60 experiments.

Table 1. Reaction of Various Alkaline Enolates with Ethyl 3-Iodopropenoates[a]



entry	Aux*	M	*E* or *Z*, **5a** or **5b**	conditions	yield (%)	*R/S*[b]	*E*/*Z*, **4a/4b**
1	Evans	Na	*E* (**5a**)	THF	81	78:22	>99:1
2	Evans	Na	*E*	CH_2Cl_2−THF[c]	95[d]	>97:3[d]	>99:1
3	Evans	K	*E*	CH_2Cl_2−tol	92	95:5	>99:1
4	Evans	Na	*Z* (**5b**)	THF	81	75:25	<1:99
5	Evans	Na	*Z*	THF, −100 °C	70	87:13	<1:99
6	Evans	Na	*Z*	tol−THF	85	88:12	<1:99
7	Evans	Na	*Z*	CH_2Cl_2−THF[c]	95[d]	>97:3[d]	<1:99
8	Nagao-I	Na	*E* (**5a**)	CH_2Cl_2−THF	0[e]		
9	Nagao-II	Na	*E*	CH_2Cl_2−THF	0[e]		
10	Oppolzer	Na	*E*	CH_2Cl_2−THF	73	>97:3	>99:1
11	Oppolzer	Li	*Z* (**5b**)	THF, −30 °C	NR		
12	Oppolzer	Na	*Z*	CH_2Cl_2−THF	22	83:17	28:72
13	Oppolzer	K	*Z*	CH_2Cl_2−tol	0[e]		
14	ours	Na	*E* (**5a**)	CH_2Cl_2−THF	95[d]	>97:3[d]	>99:1
15	ours	Na	*Z* (**5b**)	CH_2Cl_2−THF	93[d]	>97:3[d]	<1:99

[a] The commercially available THF solution of the base (1.0−1.1 equiv, but not more) was added at −78 °C (unless otherwise indicated), with a syringe, to solutions of the acylated auxiliary in the solvent indicated first; a few min later, 1.1−1.2 equiv of **5a** or **5b** in THF, CH_2Cl_2, or toluene (tol) was added (e.g., this meant a final 9:1 CH_2Cl_2−THF mixture). Within 10−15 min, full conversions were noted in most cases. [b] Ratio *R/S* for the major isomer (*Z* or *E*) by ^{1}H NMR and HPLC. [c] Under these conditions, the reaction works identically with achiral, nonsubstituted oxazolidin-2-one. [d] Ratios of 97.5 ± 0.3 to 2.5 ± 0.3 were determined by HPLC, comparing the crudes with authentic samples of the diastereomers. [e] Decomposition of the acylated auxiliary.

It is worth noting that the use of a 9:1 CH_2Cl_2−THF mixture (that is, CH_2Cl_2 with the small volume of THF arising from the base solution) is key to get a full stereocontrol (entries 2 and 7); THF alone favors the exchange of protons H_α. The Evans auxiliary performed perfectly under these conditions, with both **5a** and **5b**. These reactions were scaled up with the same outcome (see Supporting Information). On the other hand, the alkaline enolates of acylated oxazolidine-2-thione and thiazolidine-2-thione derivatives (see entries 8 and 9 for representative trials), related to those developed by Nagao et al.[8] in the 1980s and popularized more recently by Crimmins et al.,[9] are too unstable. The Oppolzer camphorsultam[10] failed when we allowed it to react

(4) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750.

(5) For a very recent review, see: (a) Maruoka, K.; Ooi, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222 (section 4). For other excellent reviews, see: (b) Krause, N.; Hoffmann-Roder, A. *Synthesis* **2001**, 171. (c) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033 (section 8). For very recent, related works, see: (d) Linton, B. R.; Reutershan, M. H.; Aderman, C. M.; Richardson, E. A.; Brownell, K. R.; Ashley, C. W.; Evans, C. A.; Miller, S. J. *Tetrahedron Lett.* **2007**, *48*, 1993 and references therein. (e) Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Catal.* **2005**, *347*, 1576 and references therein.

(6) (a) Bell, M.; Poulsen, T. B.; Jörgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3053. (b) Wang, X.; Kitamura, M.; Maruoka, K. *J. Am. Chem. Soc.* **2007**, *129*, 1038. (c) Poulsen, T. B.; Bernardi, L.; Bell, M.; Jörgensen, K A. *Angew. Chem., Int. Ed.* **2006**, *45*, 6551 and references therein. Pioneering reactions with 3-haloacrylates: (d) Smith, A. B., III; Kilenyi, S. N. *Tetrahedron Lett.* **1985**, *26*, 4419 (1,3-diketones). (e) Bruncko, M.; Crich, D. *J. Org. Chem.* **1994**, *59*, 7921 (dioxanone enolates). (f) Ma, D.; Ma, Z.; Jiang, J.; Yang, Z.; Zheng, C. *Tetrahedron: Asymmetry* **1997**, *8*, 889 (oxazolidin-5-ones).

(7) According to standard procedures. See for example: (a) Evans, D. A.; Bartrolí, X.; Shi, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127 (B enolates). (b) Evans, D. A.; Urpí, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215 (Ti enolates). (c) Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737 (Li and Na enolates).

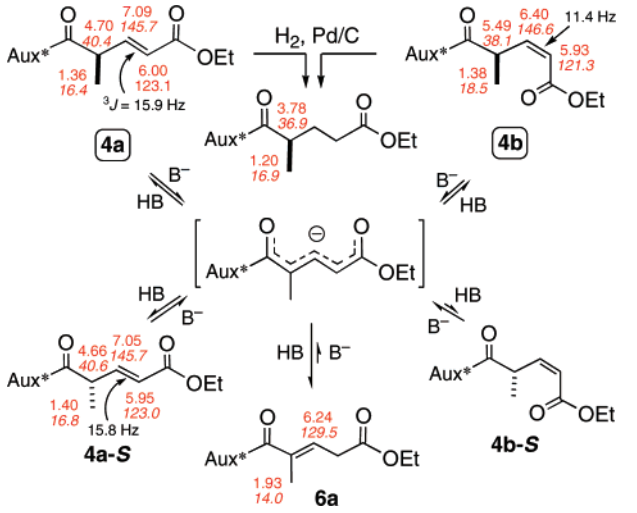
(8) (a) Nagao, Y.; Yamada, S.; Kumagai, T.; Ochiai, M.; Fujita, E. *J. Chem. Soc., Chem. Commun.* **1985**, 1418. (b) Nagao, Y.; Kumagai, T.; Yamada, S.; Fujita, E.; Inoue, Y.; Nagase, Y.; Aoyagi, S.; Abe, T. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2361. (c) Nagao, Y.; Hagiwara, Y.; Kumagai, T.; Ochiai, M.; Inoue, T.; Hashimoto, K.; Fujita, E. *J. Org. Chem.* **1986**, *51*, 2391.

with the *Z* isomer **5b** (entries 11−13). Finally, our auxiliary[11] (entries 14 and 15) was as efficient as that of the Evans group.

In general, provided that the temperature was kept at −78 °C, the presence of 10 mol % of $NaN(SiMe_3)_2$ in excess did not cause any epimerization at C_α in CH_2Cl_2−THF.

To confirm the absolute configurations of **4a** and **4b**, a sample of each was hydrogenated in MeOH, affording quickly and quantitatively the same unsaturated, known pentanedioic acid derivative (Scheme 3, top).[3,4] Compound

Scheme 3. Reactions of **4a** and **4b** (Aux* = Evans Auxiliary)

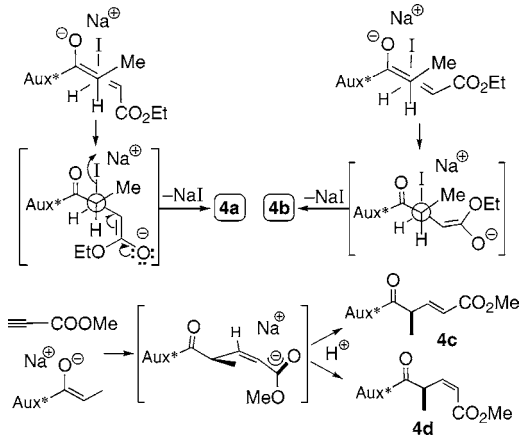


4a, treated with $Me_3SiO^-K^+$ in 1:1 CH_2Cl_2−THF at −40 °C for 14 h, followed by neutralization, gave **6a**.[12] The equilibrium mixture shown in Scheme 3 (bottom) was established, so that the thermodynamically more stable compound (**6a**) eventually predominated.

The relevance of the halogen atom was also investigated. Reactions of the Na enolates of the Evans auxiliary under the optimum conditions of entries 2 and 7 of Table 1, with the available (*E*)- and (*Z*)-3-chloropropenoate derivatives, gave in ≥95% yields only one stereoisomer in each case, with full retention of the configuration of the double bond, and which were respectively identical to the products arising from the (*E*)- and (*Z*)-3-iodoacrylates. We also checked the analogous *Z* isomer of the ethyl 3-bromopropenoate, with the same result. In short, the three halo derivatives can be used with similar efficiency.

This is reasonable for a mechanism[13a] in which the Michael addition is followed by the quick elimination of NaX from the intermediate, at −78 °C. In other words, retention of configuration at the double bond can be accounted for (see Scheme 4) by the quick departure of the leaving group with

Scheme 4. Plausible Mechanisms



a minimum rotation around the CHX−C(sp^2) single bond[13b] (the Newman projection of which is not drawn to save space).

Reaction of the Na enolate of Aux*COEt (Aux* = Evans auxiliary drawn in Table 1) with methyl propynoate (methyl propargylate), a synthetic equivalent of **5a**/**5b**, also proceeded in good yield and >97:3 dr at C_α but gave a 77:23 *Z*/*E* mixture under our standard conditions (Scheme 4, bottom) and similar mixtures under other conditions. Thus, the auxiliary controls the α stereocenter, but as 23% of the more stable *E* isomer is obtained rather than the anticipated *Z* isomer alone (arising from a *trans* addition), a ketene enolate is assumed to be the intermediate.

Standard transformations of the characteristic groups of the adducts can provide a series of chiral fragments of C-substituted five-carbon chains. Examples of these building blocks are shown in Scheme 5. Removal of the chiral auxiliary of **4a** (Aux* = Evans auxiliary shown in Table 1) with $NaBH_4$ in THF−H_2O at rt[14] gave **7a** in excellent

(9) (a) Crimmins, M. T.; King, B. W.; Tabet, E. A. *J. Am. Chem. Soc.* **1997**, *119*, 7883. (b) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775. (c) Crimmins, M. T.; Caussanel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3128 and references therein.

(10) (a) Oppolzer, W.; Chapuis, C.; Bernardinelli, G. *Helv. Chim. Acta* **1984**, *67*, 1397. (b) Oppolzer, W.; Moretti, R.; Thomi, S. *Tetrahedron Lett.* **1989**, *30*, 5603. (c) Oppolzer, W.; Blagg, J.; Rodríguez, I.; Whalter, E. *J. Am. Chem. Soc.* **1990**, *112*, 27667.

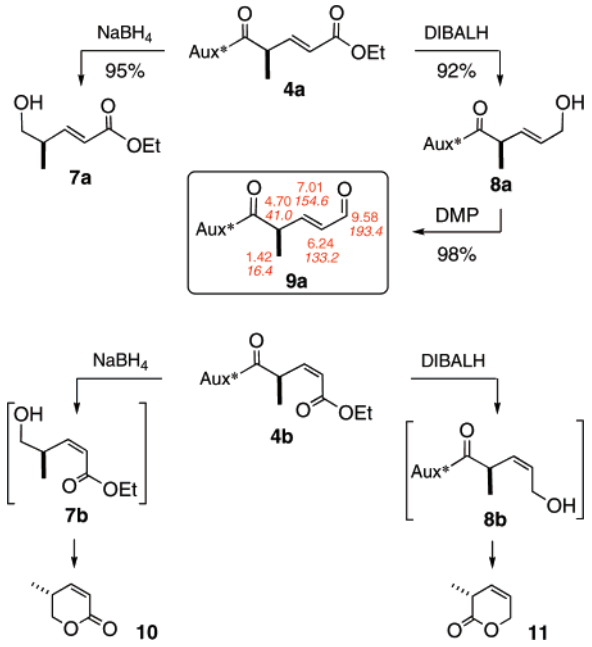
(11) (a) We prepared the *N*-propanoyl derivative of our thiazolidin-2-one by oxidation of the *N*-propanoyl-Nagao-II auxiliary with DDQ. More details and other applications of this chiral auxiliary will be reported in a future full paper. (b) Spectral data of the addition−elimination product **4a′** (isomer *E*): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, *J* = 7.0 Hz, 3H), 1.34 (d, *J*= 6.8 Hz, 3H), 2.95 (m, 2H), 3.11 (dd, *J* = 12.8 Hz, *J* = 3.6 Hz, 1H), 3.35 (dd, *J* = 12.8 Hz, *J* = 7.2 Hz, 1H), 4.20 (m, 1H), 5.93 (dd, *J* = 15.6 Hz, *J* = 1.2 Hz, 1H), 7.08 (dd, *J* = 15.6 Hz, *J* = 7.2 Hz, 1H), 7.25−7.45 (m, 5H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 14.2, 16.9, 28.5, 37.4, 41.4, 59.7, 60.5, 122.6, 127.2, 128.9, 129.4, 136.4, 146.0, 166.1, 172.2, 172.3. Spectral data of the adduct **4b′** (isomer *Z*), under the same conditions: ^{1}H NMR δ 1.28 (t, *J* = 7.2 Hz, 3H), 1.35 (d, *J* = 6.8 Hz, 3H), 2.95 (m, 2H), 3.21 (br d, *J* = 13.2 Hz, 1H), 3.30−3.35 (m, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 4.90 (m, 1H), 5.44 (m, 1H), 5.90 (dd, *J* = 11.6 Hz, *J* = 1.2 Hz, 1H), 6.37 (dd, *J* = 11.6 Hz, *J* = 8.6 Hz, 1H), 7.25−7.45 (m, 5H); ^{13}C NMR δ 14.2, 16.7, 28.6, 37.4, 39.4, 60.0, 60.3, 121.2, 127.1, 128.8, 129.4, 136.5, 146.7, 165.2, 171.5, 174.2.

(12) The reactions were followed by NMR: during the first hours, an equilibration with **4a-*S*** was noted (2:1) but eventually only **6a** was obtained. Isomer **4b** isomerized much more slowly, to yield **4a** + **4a-*S***, but after 48 h, all the isomers had also been converted to **6a** (whereas **4b-*S*** and the *Z* isomer of **6a** were not detected).

(13) (a) Classical review of $S_N(Ad_N\text{-}E)$ mechanisms in conjugate alkenes: Rappoport, Z. *Acc. Chem. Res.* **1992**, *25*, 474. (b) That is, before the equilibration among the three rotamers could take place.

(14) Prassad, M.; Har, D.; Kim, H.-Y.; Repic, O. *Tetrahedron Lett.* **1998**, *39*, 7067.

Scheme 5. Conversion of **4a** and **4b** to Various Chiral Fragments (Aux* = Evans Auxiliary)



yields,[15] operating under the following milder conditions: 140 mol % of $NaBH_4$ and 110 mol % of Na_2HPO_4 in water at 0 °C were added dropwise to **4a** in THF at 0 °C, the bath was removed, and stirring was continued for 2−3 h; otherwise, the saturated hydroxyester was obtained as a byproduct in 20−30% yields (by concomitant reduction of the conjugate double bond). On the other hand, the reduction of **4a** with an excess of DIBALH in CH_2Cl_2−hexane at −78 °C afforded **8a** selectively.[16] Oxidation of **8a** with DMP gave the desired **9a** (our true goal, as mentioned in Scheme 1), in nearly quantitative yields.

Reduction of **4b** with $NaBH_4$ under the above-mentioned conditions gave a mixture of **7b** and **10**.[17] Addition of a catalytic amount of NaH to the mixture in THF at rt converted completely **7b** into **10** within a few hours. Moreover, when the reaction of **4b** with an excess of DIBALH at −78 °C was quenched with EtOAc, allowed to warm up, and isolated, only **11**[18] and Aux*H were obtained, in ≥90% yields.

In principle, a plethora of related chiral blocks from other alkaline enolates (not only Aux*-containing enolates) and diversely substituted conjugate esters, nitriles, or ketones (X−CR═CH−COOR, X−CH═CR−CN, or X_2C═CH−COR) may be accessible by similar protocols.

In summary, we have uncovered a simple procedure to which, surprisingly, nobody had paid attention before: the Na enolates of the *N*-propanoyl derivatives of the most common auxiliary (and of our new thiazolidin-2-one auxiliary) react with ethyl 3-halopropenoates in 9:1 CH_2Cl_2−THF at −78 °C within a few minutes, to afford excellent yields of adduct **4a** or **4b** with an extraordinary stereocontrol; this is not the case when alkyl propynoates are used instead. The adducts can be manipulated appropriately to obtain a range of C1−C5 chiral building blocks (chiroblocks).

Acknowledgment. Financial support from the Spanish Ministerio de Educación y Ciencia, through the grants SAF-2002-02728 and CTQ-2006-15393, and a Ramón y Cajal Research Contract to A.M.C. are acknowledged. J.E. holds a UB studentship (Jan. 2004 to Dec. 2007) and thanks Ph.D. student Mireia Sidera, of our department, for an additional batch of **4a**. The Generalitat de Catalunya contributed partially by means of the grant 2001SGR065 (2001−2005, Grup de Síntesi Estereoselectiva d'Antibiòtics i Antivírics).

Supporting Information Available: Experimental data and copies of the ^1H and ^{13}C NMR spectra of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702632M

(15) Enantiopure **7a** had been obtained from D-mannitol by a sequence that includes an epoxide opening, with $AlMe_3$, in the last step: Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. *Tetrahedron Lett.* **1997**, *38*, 3419.

(16) We could not stop the reduction at the aldehyde stage, but to a mixture of alcohol and aldehyde, using low amounts of DIBALH and other solvents, as well as operating even at −100 °C.

(17) The racemic form of **10** is a known compound: (a) Dieter, R. K.; Guo, F. *Org. Lett.* **2006**, *8*, 4779 and references therein. (b) We have measured an $[\alpha]_D$ value of −6.0 (*c* 0.60, $CHCl_3$) for our sample.

(18) Known in its racemic form: (a) Andreana, P. R.; McLellan, J. S.; Chen, Y.; Wang, P. G. *Org. Lett.* **2002**, *4*, 3875 and references therein. (b) We have measured an $[\alpha]_D$ value of −52.7 (*c* 0.80, $CHCl_3$) for **11**.