Secondary Allyltitanium(IV) Reagents in Aldehyde Allylation I: Extension of the Hoppe Reaction to γ-Alkoxy Secondary Allyl Carbamates

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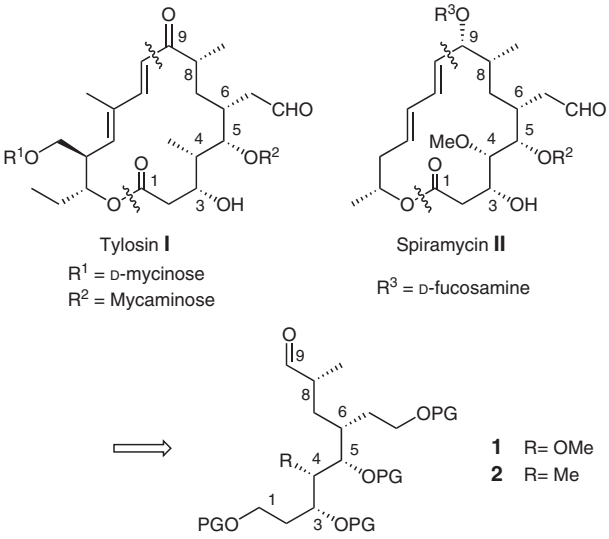
Abstract: An efficient access to optically active (*R*)- or (*S*)-γ-alkoxy allyltitanium(IV) intermediates, in aldehyde allylation reactions, is described. Enantiomeric γ-alkoxy secondary allyl carbamates (*R*)- and (*S*)-**14** were first prepared. Determination of their enantiomeric excess was realised on the corresponding deuterated isotopic derivatives by NMR in chiral liquid media. Subsequent aldehyde allylation reaction with propanal performed under Hoppe *n*-BuLi·(–)-sparteine/Ti(O*i*-Pr)$_4$ or *n*-BuLi·TMEDA/Ti(O*i*-Pr)$_4$ conditions, led to both enantiomeric homoallylic alcohols **15** or *ent*-**15** in 90% yield, 100% ed and 80% ee.

Key words: Hoppe allylation, allyltitanium reagent, ^{1}H NMR chiral nematic solvent, Sharpless resolution

In the past decades, several 14- and 16-membered macrolide antibiotics have been isolated or synthesised, which proved to be important therapeutic agents. In the same time, aldehyde allylation and aldolisation reactions have become the best tools for the diastereoselective and enantioselective construction of 1,2- and 1,3-diol systems. As a consequence, many efforts were devoted towards the total synthesis of several compounds in the important erythromycin family,[1] such as tylosin (**I**)[2] or spiramycin (**II**),[3] for either veterinary or clinical use (Scheme 1).

We described earlier a synthetic approach to a C1-C9 eastern part **2** of tylosin (**I**),[4] based on sequential Hoppe aldehyde allylation[5] reaction (Scheme 2). The original Hoppe allylation involved the reaction of the crotyltitanium(IV) derivative (*R*)-**'Ti'-I** on the *Si* face of aldehyde, to give, with propanal for example, the homoallylic alcohol (*Z*)-*anti*-**4** in 90% yield, 100% de, and 92% ee (Scheme 2). This (*R*)-**'Ti'-I** intermediate was formed in situ from the achiral primary crotyl carbamate **3**, after crystallisation of the (*S*)-**'Li'-I** sparteine complex (second order asymmetric induction) and transmetallation with Ti(O*i*-Pr)$_4$.

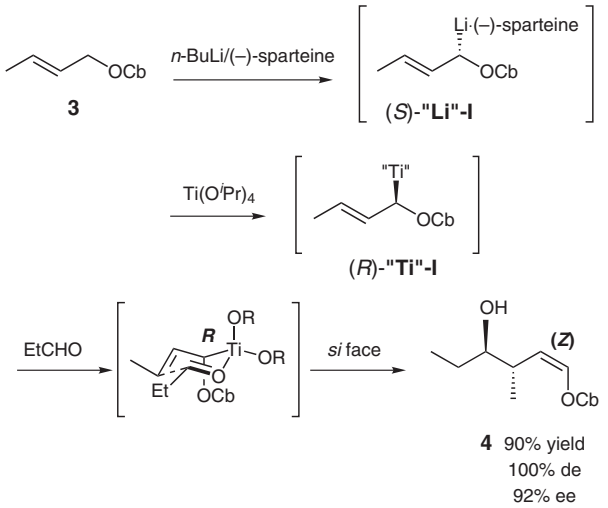
In our previous preparation of the C1-C9 eastern part **8** of tylosin (**I**), from optically active aldehyde **7** (**7** → **8**), the Hoppe allylation invoked the reaction of the same crotyltitanium derivative (*R*)-**'Ti'-I** for introduction of the



Scheme 1

methyl group at C8 centre in a double stereodifferentiation (Scheme 3).[4]

However, the installation of the side chain in C6 together with introduction of the hydroxyl function at C5 in the right configuration (**5** → **6**) was a real challenge. The optically pure γ-alkoxy allyltitanium(IV) derivative (*R*)-



Scheme 2[5]

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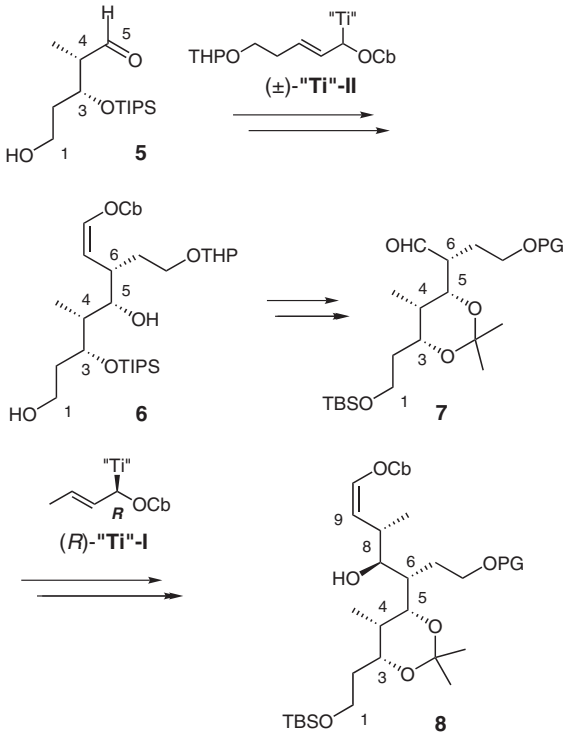
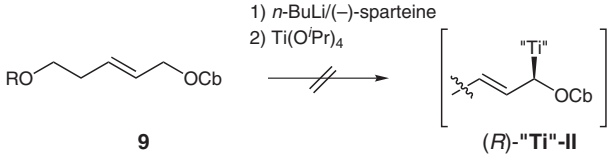


Scheme 3

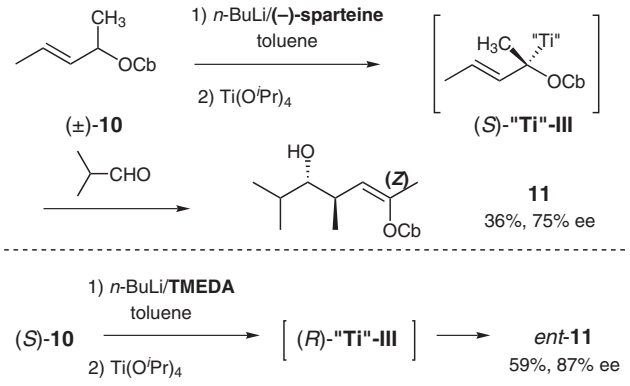
'Ti'-II cannot be prepared, via the corresponding lithio derivative of carbamate **9**, either by an enantioselective deprotonation or a second-order asymmetric induction, as for the (*R*)-**'Ti'-I** reagent[4,5] (Scheme 4).



Scheme 4

To circumvent this difficulty, the side chain was introduced using the racemic (±)-**'Ti'-II** reagent under kinetic resolution. Nevertheless, in order to develop a general aldehyde allylation reaction from γ-alkoxy allyltitanium derivatives, we turned our attention to the results published by Hoppe about secondary crotylcarbamates, and to our surprise, not used at this time in total synthesis.[6]

In this important work (Scheme 5), Hoppe[6] has shown that when the racemic secondary crotylcarbamate (±)-**10** was treated under classical conditions [*n*-BuLi·(–)-sparteine/Ti(O*i*-Pr)$_4$], and reacted with an achiral aldehyde, such as isobutyraldehyde, only the (*Z*)-*anti* homoallylic alcohol **11** was obtained in 36% yield and 75% ee by enantiomer-differentiating deprotonation. Similarly, starting from the (*S*)-**10** enantiomer, Hoppe has demonstrated that using BuLi·TMEDA/Ti(O*i*-Pr)$_4$ sequence, only the adduct *ent*-**11** was isolated, generated from the (*R*)-**'Ti'-III** derivative (Scheme 5).



Scheme 5[6]

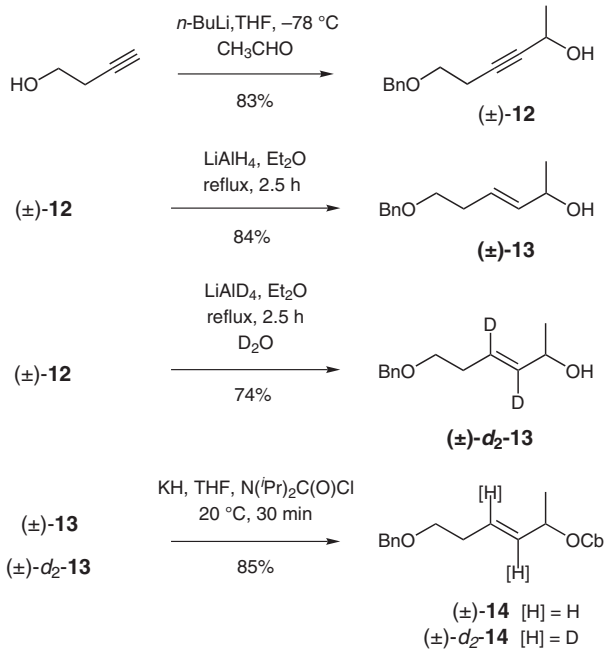
These results indicate that transmetallation reaction Li → Ti with Ti(O*i*-Pr)$_4$ occurred with inversion of configuration when *n*-BuLi·(–)-sparteine/Ti(O*i*-Pr)$_4$ route was used; retention was observed under application of *n*-BuLi·(–)-TMEDA/Ti(O*i*-Pr)$_4$ conditions.

Taking advantage of this work, we wanted to get an access to optically active (*R*) or (*S*)-γ-alkoxy allyltitanium (IV) intermediates to realise aldehyde allylation reactions, under simple asymmetric induction or double stereodifferentiation. For this purpose, preparation of enantiomeric allyl carbamates (*R*)- and (*S*)-**14** was needed.

However, in these series, enantiomeric excess could not be measured by classical NMR analysis, using derivatisation or Europium shifts. Consequently, we turned to an alternative method based on NMR in chiral liquid crystal media developed by Courtieu.[7] For this study which involved an observation of the deuterium element, we synthesised the corresponding deuterated isotopic derivatives.

First, racemic propargylic alcohol (±)-**12** was obtained from commercial butynol: after benzylation, an homologation was effected with acetaldehyde (83% yield); the triple bond of (±)-**12** was then reduced with $LiAlH_4$ to give the (*E*)-allylic alcohol (±)-**13** in 84% yield (Scheme 6). For an access to the corresponding (±)-d_2-**13** compound, the reduction was carried out using $LiAlD_4$ and quenching with D_2O (74% yield). Carbamoylation of (±)-**13** or (±)-d_2-**13** was then carried out using KH/THF/N(*i*-Pr)$_2$COCl conditions to deliver carbamate (±)-**14** or (±)-d_2-**14** [Cb = CON(*i*-Pr)$_2$] in 85% yield.

Optically active allylic alcohols (*S*)-**13** or (*S*)-d_2-**13** and (*R*)-**13** or (*R*)-d_2-**13** were then synthesised by application of the enantioselective Sharpless epoxidation reaction in a kinetic resolution strategy.[8] Starting from alcohol (±)-**13**, and using (–)-diisopropyl D-tartrate, the (*S*)-**13** allylic alcohol enantiomer was obtained in 38% yield (Scheme 7). When (+)-diisopropyl L-tartrate was employed, kinetic resolution furnished the enantiomer (*R*)-**13** in 36% yield. Allyl carbamates (*R*)- and (*S*)-**14** were then prepared from alcohols (*R*)-and (*S*)-**13** under KH, THF, N(*i*-Pr)$_2$COCl conditions. Using the same sequence, alcohol (±)-d_2-**13** delivered respectively the (*S*)-d_2-**13** and (*R*)-d_2-**13** allylic



Scheme 6

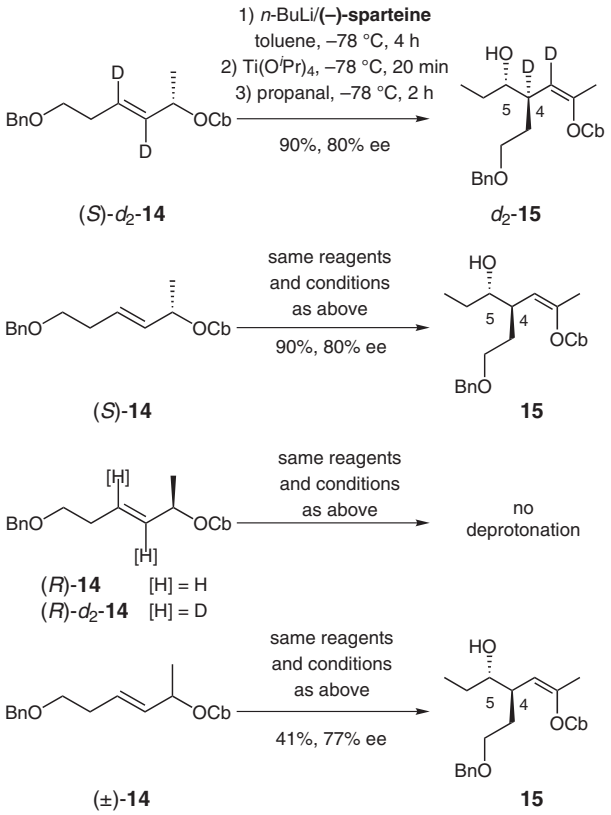
alcohols and the corresponding allyl carbamates (*S*)-d_2-**14** and (*R*)-d_2-**14**.

Application of the NMR chiral liquid crystal media analysis led us to determine an enantiomeric excess of 95% for (*S*)- and (*R*)-d_2-**13** and (*S*)- and (*R*)-d_2-**14** allylic derivatives.

Having in our hands all racemic and optically active γ-alkoxycarbamates **14**, we investigated the aldehyde allylation reaction. First, it was shown that both racemic carbamates (±)-**14** and (±)-d_2-**14** treated under *n*-BuLi·TMEDA/Ti(O*i*-Pr)$_4$ conditions led, after reaction with propanal, to the expected (*Z*)-*anti*-homoallylic alcohols (±)-**15** and (±)-d_2-**15** in 90% yield and a total diastereoselectivity.

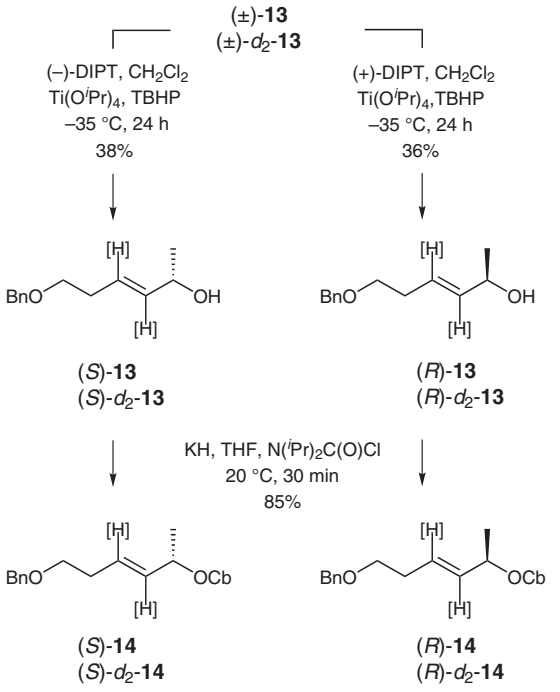
When *n*-BuLi·(–)-sparteine/Ti(O*i*-Pr)$_4$ sequence was applied to the (*S*)-d_2-**14** allyl carbamate, in the reaction with propanal under simple asymmetric induction, the expected d_2-**15** adduct was isolated in 90% yield (Scheme 8); this compound d_2-**15** had a 80% enantiomeric excess (measured by NMR in chiral liquid crystal media or by classical NMR shift experiments with Europium salts Eu(hfc)$_3$). Reaction with carbamate (*S*)-**14** under the same method led to the homoallylic alcohol **15** in an equivalent chemical yield (90%) and ee (80%).

A complementary experiment was also carried out from (*R*)-**14** or (*R*)-d_2-**14**. Using *n*-BuLi·(–)-sparteine/Ti(O*i*-Pr)$_4$ conditions, no deprotonation was observed and the starting material was recovered. Finally, when carbamate (±)-**14** was treated under the same route, only the homoallylic alcohol **15** was isolated in 41% yield and 77% enantiomeric excess under kinetic resolution by enantiomer-differentiating deprotonation (Scheme 8).

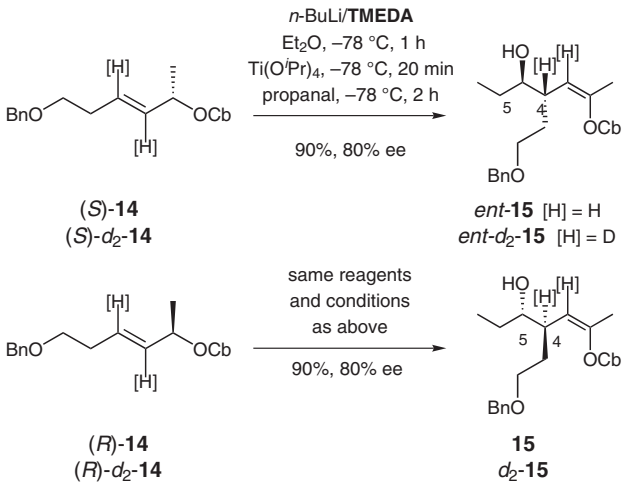


Scheme 8

When *n*-BuLi·TMEDA/Ti(O*i*-Pr)$_4$ route was applied to the (*S*)-d_2-**14** and (*S*)-**14** allyl carbamates, homoallylic alcohols *ent*-d_2-**15** and *ent*-**15** were isolated in 90% yield (Scheme 9); as above a 80% enantiomeric excess was measured.



Scheme 7



Scheme 9

In conclusion, in this work, the Hoppe allylation was extended to the γ-alkoxy secondary allyl carbamates (*S*)- and (*R*)-**14**. We developed here an efficient route to prepare (*S*)- or (*R*)-γ-alkoxy secondary allyltitanium intermediates. With achiral aldehydes, in simple induction, corresponding homoallylic alcohols are obtained in good chemical yield, total diastereoselectivity and 80% ee.

Now, we expected that these titanium reagents exhibit a high degree of reagent-control with chiral aldehydes; therefore, we turned our efforts to an application in a synthetic approach to the eastern part **1** of spiramycin (**II**).[9]

All air and/or H_2O sensitive reactions were carried out under argon, with freshly distilled anhyd solvents using standard syringe-cannula/septa technique. All corresponding glassware was oven dried (110 °C) and/or carefully dried in line with a flameless heat gun. THF, Et_2O, toluene were distilled from sodium-benzophenone; CH_2Cl_2, pentane, cyclohexane were distilled from CaH_2; TMEDA, (–)-sparteine, Ti(O*i*-Pr)$_4$ were distilled prior to use. All reactions were monitored by TLC carried out on precoated plates of silica gel 60F 254 (Merck, Art. 7735). Visualisation was accomplished with UV light then 10% ethanolic phosphomolybdic acid solution followed by heating. Flash chromatography was performed on silica gel Merck, 60, 230–400 mesh (Art. 9385). NMR spectra were recorded in $CDCl_3$.

Enantiomeric excess were measured in $CDCl_3$ by ^{1}H NMR chemical shift at 400 MHz with Eu(hfc)$_3$: a solution of Eu(hfc)$_3$ 10 mg/mL in $CDCl_3$ was added to a sample of 2 to 5 mg of title compound in $CDCl_3$ up to significant splitting of signals. Alternatively, enantiomeric excess were measured by ^{2}D NMR chemical shift at 400 MHz in polybenzyl-L-glutamate with CH_2Cl_2 as solvent: 80 to 100 mg of polybenzyl-L-glutamate and 25 to 50 mg of deuterated title compound in a NMR tube were dissolved in 0.5 mL of CH_2Cl_2. The sample was centrifuged until forming a solid crystal liquid phase. ^{2}D NMR spectra were then recorded.

Optical rotations were determined at 20 °C in MeOH, 589 nm, on a Perkin-Elmer 241 instrument or a JASCO DIP 370 instrument. Bulbs to bulbs distillations were performed using a Büchi GKR 51 Kugelrohr apparatus.

(2*R*/*S*)-6-(Benzyloxy)hex-3-yn-2-ol [(±)-12]

To a suspension of NaH (60% in oil, 13.7 g, 342 mmol, 1.2 equiv) in anhyd THF (120 mL) at 0 °C, was slowly added a solution of but-3-yn-1-ol (20 g, 285 mmol) in Et_2O (120 mL) and the mixture was stirred for 20 min at 20 °C. To this mixture were added a solution of benzyl bromide (37.3 g, 313.5 mmol, 1.1 equiv) in anhyd THF (60 mL) and NaI (0.5 g). After stirring for 8 h at 20 °C, the mixture was treated at 0 °C with 1 M aq HCl (75 mL) and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The oily residue was purified by distillation to give the 4-(benzyloxy)butyne as a colourless oil (42.9 g, 94%); bp 83 °C/2 mbar.

4-(Benzyloxy)butyne

IR (CCl_4): 3329, 3040, 2216 cm^{-1}.

^{1}H NMR (270 MHz): δ = 2.01 (t, *J* = 2.5 Hz, 1 H, H-1), 2.55 (td, *J* = 7.0, 2.5 Hz, 2 H, CH_2-3), 3.62 (t, *J* = 7.0 Hz, 2 H, CH_2-4), 4.56 (s, 2 H, PhCH_2), 7.21–7.42 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 19.7 (CH_2-3), 65.2 (CH_2-4), 68.9 (CH-1), 73.2 (Ph*C*H$_2$), 81.1 (C-2), 127.4 (2 CH, C_6H_5), 128.2 (2 CH, C_6H_5), 128.5 (CH, C_6H_5), 138.6 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 161 (MH^+).

To a solution of 4-(benzyloxy)butyne (see above) (25 g, 155 mmol) in anhyd THF (150 mL) at –78 °C was slowly added *n*-BuLi (1.6 M in hexane, 106.7 mL, 171 mmol, 1.1 equiv). After stirring for 20 min, acetaldehyde (21.9 mL, 0.388 mmol, 2.5 equiv) was added. The reaction mixture was then allowed to slowly warm to r.t. and after stirring for 1 h, aqueous 1 M HCl (100 mL) was added. After extraction with Et_2O, drying (Na_2SO_4) and filtration, the solvents were removed under reduced pressure. The crude oil was purified by flash chromatography on silica gel (hexane–EtOAc, 80:20) to give the alcohol (±)-**12** as a colourless oil (26.2 g, 83%).

(±)-12

IR (KBr): 3388, 2250 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.42 (d, *J* = 6.6 Hz, 3 H, CH*C*H$_3$), 2.52 (td, *J* = 6.9, 2.0 Hz, 2 H, CH_2-5), 3.67 (t, *J* = 6.9 Hz, 2 H, CH_2-6), 4.65 (s, 2 H, PhCH_2), 4.24 (qt, *J* = 6.6, 2.0 Hz, 1 H, C*H*CH$_3$), 7.44 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 20.1 (CH_2-5), 24.6 (CH*C*H$_3$), 58.5 (*C*HCH$_3$), 68.3 (CH_2-6), 73.0 (Ph*C*H$_2$), 81.2 and 83.4 (C≡C), 127.8 and 128.5 (5 CH, C_6H_5), 138.0 (C, C_6H_5).

MS (CI, NH_3): *m*/*z* = 222 (MH^+ + 17).

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.52; H, 7.98.

(3*E*,*R*/*S*)-6-(Benzyloxy)hex-3-en-2-ol [(±)-13]

To a solution of the alcohol (±)-**12** (26.2 g, 128 mmol) in anhyd Et_2O (140 mL) at 0 °C was slowly added a 1 M solution of $LiAlH_4$ in THF (141 mL, 141 mmol, 1.1 equiv). The reaction mixture was placed in a preheated bath and refluxed for 2.5 h. The solution was then cooled at 0 °C, and carefully and successively treated with H_2O (50 mL), aq 10 M solution of NaOH (12.5 mL), and H_2O (25 mL). The precipitate was filtered and washed with Et_2O. The filtrate was concentrated under reduced pressure and purified by flash chromatography on silica gel (hexane–EtOAc, 50:50) to give the title compound (±)-**13** as a colourless oil (22.5 g, 84%); bp 130 °C/0.03 mbar.

IR (CCl_4): 3387 cm^{-1}.

^{1}H NMR (250 MHz): δ = 1.26 (d, *J* = 6.4 Hz, 3 H, CH_3-1), 2.36 (td, *J* = 6.6, 5.8 Hz, 2 H, CH_2-5), 3.52 (t, *J* = 6.6 Hz, 2 H, CH_2-6), 4.28 (qd, *J* = 6.4, 5.2 Hz, 1 H, CH-2), 4.52 (s, 2 H, PhCH_2), 5.56 (dd, *J* = 15.5, 5.2 Hz, 1 H, =CH-3), 5.74 (dt, *J* = 15.5, 5.8 Hz, 1 H, =CH-4), 7.32 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 23.4 (CH_3-1), 32.6 (CH_2-5), 68.8 (CH*C*H$_3$), 69.7 (CH_2-6), 72.9 (Ph*C*H$_2$), 127.1 (=CH, C-4), 127.6

(CH, C_6H_5), 127.8 (2 CH, C_6H_5), 128.4 (2 CH, C_6H_5), 136.3 (=CH, C-3), 138.4 (C, C_6H_5).

MS (CI, NH_3): *m/z* = 207 (MH^+).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.74; H, 8.98.

(2*R*,3*E*)-6-(Benzyloxy)hex-3-en-2-ol [(*R*)-13]; Typical Procedure

To a solution of diisopropyl L-(+)-tartrate (10.13 g, 43.2 mmol, 1 equiv) in freshly distilled anhyd CH_2Cl_2 (220 mL) was added freshly distilled Ti(O*i*-Pr)$_4$ (10.7 mL, 36 mmol, 0.83 equiv). After stirring for 20 min at r.t., the reaction mixture was cooled at –35 °C (bath temperature) and a solution of the alcohol (±)-**13** (8.9 g) in anhyd CH_2Cl_2 (220 mL) was added via canula. After stirring for 1 h, a 5.5 M solution of *tert*-butyl hydroperoxide in decane (4.17 mL, 23 mmol, 0.53 equiv) was slowly added. The stirring was maintained for 24 h at –35 °C, and the mixture was then quenched at r.t. by addition of 10% aq solution of citric acid (200 mL). After 3 h, the solution was filtered through a pad of Celite, the Celite pad was washed with Et_2O and the aqueous phase was extracted with Et_2O. The combined Et_2O layers were concentrated under reduced pressure and the residue was diluted in Et_2O (120 mL) and a 7.5 M solution of NaOH in H_2O (120 mL) was added. After 6 h, the organic phase was separated, washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was flash chromatographed on silica gel (cyclohexane–EtOAc, 60:40) and purified further by bulb to bulb distillation to give the title compound (*R*)-**13** as a colourless oil (3.2 g, 36%); $[\alpha]_D$ +20 (*c* = 1.03, MeOH).

(2*S*,3*E*)-6-(Benzyloxy)hex-3-en-2-ol [(*S*)-13]

The enantiomeric compound (*S*)-**13** was obtained by the same procedure using diisopropyl D-(–)-tartrate in 38% yield; $[\alpha]_D$ –22 (*c* = 1.35, MeOH).

(2*R/S*,3*E*)-6-(Benzyloxy)-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}hexene [(±)-14], (2*R*,3*E*)-6-(Benzyloxy)-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}hexene [(*R*)-14], and (2*S*,3*E*)-6-(Benzyloxy)-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}hex-3-ene [(*S*)-14]; Typical Procedure

To a suspension of KH (30% in oil, 5.88 g, 44 mmol, 1.4 equiv) in anhyd THF (40 mL) at 0 °C, was slowly added a solution of alcohol (±)-**13**, or (*R*)-**13**, or (*S*)-**13** (6.5 g, 31.4 mmol) in THF (35 mL). The resulting solution was stirred for 20 min at 20 °C and a solution of diisopropylcarbamoyl chloride (5.63 g, 34.5 mmol, 1.1 equiv) in anhyd THF (25 mL) was added. After stirring for 30 min at 20 °C, the mixture was treated at 0 °C with 1 M aq HCl (40 mL) and extracted with Et_2O. The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The oily residue was purified by flash chromatography on silica gel (hexane–EtOAc, 80:20) or distillation to give the title compound (±)-**14** or (*R*)-**14** or (*S*)-**14** as a colourless oil (8.92 g, 85%); bp 140 °C/0.04 mbar.

IR (CCl_4): 1688 cm^{-1}.

^{1}H NMR (250 MHz): δ = 1.18 {d, *J* = 6.8 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.30 (d, *J* = 6.4 Hz, 3 H, CH_3-1), 2.35 (q, *J* = 6.8 Hz, 2 H, CH_2-5), 3.49 (t, *J* = 6.8 Hz, 2 H, CH_2-6), 3.60–4.2 {wide m, 2 H, N[C*H*(CH$_3$)$_2$]$_2$}, 4.52 (s, 2 H, PhCH_2O), 5.27 (quint, *J* = 6.4 Hz, 1 H, H-2), 5.63 (dt, *J* = 15.9, 6.8 Hz, 1 H, =CH-4), 5.64 (dd, *J* = 15.9, 6.4 Hz, 1 H, =CH-3), 7.32 (m, 5 H, C_6H_5).

^{13}C NMR (62.5 MHz): δ = 20.7 and 21.1 {4 CH_3, N[CH(*C*H$_3$)$_2$]$_2$}, 26.8 (CH_3-1), 32.7 (CH_2-5), 45.6 {2 CH, N[*C*H(CH$_3$)$_2$]$_2$}, 69.6 (CH_2-6), 70.8 (CH-2), 72.8 (Ph*C*H$_2$), 127.5 (=CH-4), 127.6 and 128.3 (5 CH, C_6H_5), 132.6 (=CH-3), 138.5 (C, C_6H_5), 155.2 (C=O).

MS (CI, NH_3): m/z = 334 (MH^+).

Anal. Calcd for $C_{20}H_{31}NO_3$: C, 72.04; H, 9.37; N, 4.20. Found: C, 72.18; H, 9.48; N, 4.22.

(*R*)-14

$[\alpha]_D$ –6.5 (*c* = 2.00, MeOH).

(*S*)-14

$[\alpha]_D$ +6.8 (*c* = 2.05, MeOH).

(3*E*,3*d*,4*d*)-6-(Benzyloxy)hex-3-en-2-ol [(±)-*d*$_2$-13]

To a solution of alcohol (±)-**12** (11.04 g, 69 mmol) in anhyd Et_2O (80 mL) at 0 °C was slowly added a 1 M solution of $LiAlD_4$ in THF (83 mL, 83 mmol, 1.2 equiv). The reaction mixture was placed in a preheated bath and refluxed for 2.5 h. The solution was then cooled to 0 °C, and carefully and successively treated with D_2O (98%-*d*, 27.5 mL, 1.37 mol, 20 equiv), 10 M aq solution of NaOH (7 mL), and H_2O (15 mL). The precipitate was filtered and washed with Et_2O. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel (hexane–EtOAc, 50:50) to give the title compound (±)-*d*$_2$-**13** as a colourless oil (10.6 g, 74%).

IR (CCl_4): 3387 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.26 (d, *J* = 6.4 Hz, 3 H, CH_3-1), 1.74 (s, 1 H, OH), 2.36 (t, *J* = 6.6 Hz, 2 H, CH_2-5), 3.52 (t, *J* = 6.6 Hz, 2 H, CH_2-6), 4.27 (q, *J* = 6.4 Hz, 1 H, CH-2), 4.52 (s, 2 H, PhCH_2), 7.35 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 23.2 (CH_3-1), 32.3 (CH_2-5), 68.5 (CH-2), 69.6 (CH_2-6), 72.8 (Ph*C*H$_2$), 126.4 (3 signals, CD, *J* = 23.2 Hz, C-4), 127.6 (CH, C_6H_5), 127.7 (2 CH, C_6H_5), 128.4 (2 CH, C_6H_5), 135.8 (3 signals, CD, *J* = 23.2 Hz, C-3), 138.4 (C, C_6H_5).

Anal. Calcd for $C_{13}H_{16}D_2O_2$: C, 77.96; H, 9.68. Found: C, 78.04; H, 9.74.

(2*R*,3*E*,3*d*,4*d*)-6-(Benzyloxy)hex-3-en-2-ol [(*R*)-*d*$_2$-13] and (2*S*,3*E*,3*d*,4*d*)-6-(Benzyloxy)hex-3-en-2-ol [(*S*)-*d*$_2$-13]

Starting from (±)-*d*$_2$-**13**, compounds (*S*)-*d*$_2$-**13** and (*R*)-*d*$_2$-**13** were obtained by Sharpless kinetic resolution method using the same typical procedure described above for the preparation of (*R*)-**13**. Enantiomeric excess were measured by ^{2}D NMR in PBLG and found to be superior to 95%. See above for spectroscopic data.

(*R*)-*d*$_2$-13

$[\alpha]_D$ +4.5 (*c* = 2.05, MeOH).

(*S*)-*d*$_2$-13

$[\alpha]_D$ –4.3 (*c* = 2.00, MeOH).

(2*R*,3*E*,3*d*,4*d*)-6-(Benzyloxy)-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}hex-3-ene [(*R*)-*d*$_2$-14], (2*S*,3*E*,3*d*,4*d*)-6-(Benzyloxy)-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}hex-3-ene [(*S*)-*d*$_2$-14]

Compounds (*R*)-*d*$_2$-**14** and (*S*)-*d*$_2$-**14** were obtained from (*R*)-*d*$_2$-**13** and (*S*)-*d*$_2$-**13** in 85% yield, each by the same carbamoylation procedure used before to prepare (*R*)-**14** and (*S*)-**14**.

IR (CCl_4): 1688 cm^{-1}.

^{1}H NMR (270 MHz): δ = 1.20 {d, *J* = 6.9 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.31 (d, *J* = 6.6 Hz, 3 H, CH_3-1), 2.37 (t, *J* = 6.9 Hz, 2 H, CH_2-5), 3.51 (t, *J* = 6.9 Hz, 2 H, CH_2-6), 3.60–4.20 {wide m, 2 H, N[C*H*(CH$_3$)$_2$]$_2$}, 4.52 (s, 2 H, PhCH_2), 5.29 (q, *J* = 6.6 Hz, 1 H, H-2), 7.33 (m, 5 H, C_6H_5).

^{13}C NMR (67.8 MHz): δ = 20.7 and 21.1 {4 CH_3, N[CH(*C*H$_3$)$_2$]$_2$}, 26.9 (CH_3-1), 32.7 (CH_2-5), 45.6 {2 CH, N[*C*H(CH$_3$)$_2$]$_2$}, 69.7 (CH_2-6), 70.8 (CH-2), 72.9 (Ph*C*H$_2$), 127.6 and 128.4 (5 CH, C_6H_5), 132.2 (3 signals, CD, *J* = 23.2 Hz, C-3), 138.5 (C, C_6H_5), 155.2 (C=O). C-4 was not observed.

MS (CI, NH_3): *m/z* = 336 (MH^+).

Anal. Calcd for $C_{20}H_{29}D_2NO_3$: C, 71.60; H, 9.91; N, 4.18. Found: C, 71.72; H, 10.12; N, 4.15.

(*R*)-d_2-14

$[\alpha]_D$ –2.0 (*c* = 2.10, MeOH).

(*S*)-d_2-14

$[\alpha]_D$ +1.8 (*c* = 2.00, MeOH).

(2*Z*,4*R,5*S**)-4-[2-(Benzyloxy)ethyl]-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxy-hept-2-ene [(±)-15], (2*Z*,4*R*,5*S*)-4-[2-(Benzyloxy)ethyl]-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxyhept-2-ene (15) and (2*Z*,4*S*,5*R*)-4-[2-(Benzyloxy)ethyl]-2-{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxyhept-2-ene [*ent*-15]; Typical Procedures**

Racemic Homoallylic Alcohol (±)-15 from Racemic Carbamate (±)-14

To a solution of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA, 0.45 mL, 3 mmol, 2.0 equiv) in anhyd Et_2O (10 mL) at –78 °C, under argon, was added *n*-BuLi (1.6 M in hexane, 1.9 mL, 3 mmol, 2.0 equiv). After stirring for 20 min at –78 °C, a solution of the racemic allyl carbamate (±)-**14** (500 mg, 1.5 mmol) in anhyd Et_2O (3 mL), was slowly added. The solution turned pale yellow. After stirring for 1 h at –78 °C, Ti(O*i*-Pr)$_4$ (1.33 mL, 4.5 mmol, 3 equiv) was rapidly added and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, freshly distilled propionaldehyde (0.65 mL, 9 mmol, 6 equiv) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of 3 M aq HCl (20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach to 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound (±)-**15** as a pale yellow oil (520 mg, 90%).

Optically Active Homoallylic Alcohol 15 from Carbamate (*S*)-14

To a solution of (–)-sparteine (705 mg, 3 mmol, 2.0 equiv) in anhyd pentane (10 mL) at –78 °C under argon , was added a solution of the optically active allyl carbamate (*S*)-**14** (500 mg, 1.5 mmol) in anhyd pentane (3.0 mL). After stirring for 20 min at –78 °C, *n*-BuLi (1.6 M in hexane, 1.9 mL, 3 mmol, 2.0 equiv) was slowly added. The solution turned pale yellow. After stirring for 4 h at –78 °C, precooled Ti(O*i*-Pr)$_4$ (1.33 mL, 4.5 mmol, 3 equiv) in pentane (5.0 mL) was rapidly added via cannula and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, freshly distilled propionaldehyde (0.65 mL, 9 mmol, 6 equiv) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach to 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound **15** as a pale yellow oil (520 mg, 90% yield, 80% ee).

Optically Active Homoallylic Alcohol 15 from Racemic (±)-14

To a solution of (–)-sparteine (705 mg, 3 mmol, 2.0 equiv) in anhyd pentane (10 mL) at –78 °C under argon, was added a solution of the racemic allyl carbamate (±)-**14** (500 mg, 1.5 mmol) in anhyd pentane (3.0 mL). After stirring for 20 min at –78 °C, *n*-BuLi (1.6 M in hexane, 1.9 mL, 3 mmol, 2.0 equiv), was slowly added. The solution turned pale yellow. After stirring for 4 h at –78 °C, a solution of precooled Ti(O*i*-Pr)$_4$ (1.33 mL, 4.5 mmol, 3 equiv) in pentane (5.0 mL) was rapidly added via cannula and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, freshly distilled propionaldehyde (0.65 mL, 9 mmol, 6 equiv) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach to 20 °C and the resulting solution was eventually filtered on a pad of Celite to removed titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30) to give the title compound **15** as a pale yellow oil (236 mg, 41% yield, 77% ee).

Optically Active Compound *ent*-15 from Optically Active Carbamate (*S*)-14

To a solution of TMEDA (0.45 mL, 3 mmol, 2.0 equiv) in anhyd Et_2O–cyclohexane (10 mL/1.0 mL) at –78 °C, under argon, was added *n*-BuLi (1.6 M in hexane, 1.9 mL, 3 mmol, 2.0 equiv). After stirring for 20 min at –78 °C, a solution of the optically active allyl carbamate (*S*)-**14** (500 mg, 1.5 mmol) in anhyd pentane (3.0 mL), was slowly added. The solution turned pale yellow. After stirring for 1 h at –78 °C, precooled Ti(O*i*-Pr)$_4$ (1.33 mL, 4.5 mmol, 3 equiv) in pentane (5.0 mL) at –78 °C was rapidly added via cannula and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, freshly distilled propionaldehyde (0.65 mL, 9 mmol, 6 equiv) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirring mixture of aq 3 M HCl (20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to removed titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30), to give the title compound *ent*-**15** as a pale yellow oil (520 mg, 90% yield, 80% ee).

Enantiomeric Homoallylic Alcohol 15

The same procedure was used for the (*R*)-**14** enantiomer, which gave the enantiomeric homoallylic alcohol **15** with the same enantiomeric excess. Enantiomeric excess values were determined by NMR shift experiment with europium salts Eu(hfc)$_3$.

IR (CCl_4): 3395, 1715 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3-7), 1.23 {d, *J* = 7.2 Hz, 12 H, 4 CH_3, N[CH(CH_3)$_2$]$_2$}, 1.43 (m, 1 H, H_a-6), 1.55 (m, 1 H, H_a-1′), 1.57 (m, 1 H, H_b-6), 1.83 (dq, *J* = 14, 5.5 Hz, 1 H, H_b-1′), 1.93 (s, 3 H, CH_3-1), 2.51 (tt, *J* = 10.5, 5.5 Hz, 1 H, H-4), 3.40 (td, *J* = 6.5, 5.5 Hz, 1 H, H-5), 3.45 (dt, *J* = 9.3, 5.5 Hz, 1 H, H_a-2′), 3.55 (dt, *J* = 9.3, 5.5 Hz, 1 H, H_b-2′), 3.82 [br m, 1 H, NC*H*(CH$_3$)$_2$], 4.03 [br m, 1 H, NC*H*(CH$_3$)$_2$], 4.51 (s, 2 H, PhCH_2), 4.91 (d, *J* = 10.5 Hz, 1 H, =CH-3), 7.32 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 9.6 (CH_3-7), 20.3 {4 CH_3, N[CH(*C*H$_3$)$_2$]$_2$}, 26.9 (CH_3-1), 27.8 (CH_2-6), 32.2 (CH_2-1′), 39.0 (CH-4), 45.9 and 46.7 {2 CH, N[*C*H(CH$_3$)$_2$]$_2$}, 68.7 (CH_2-2′), 73.1 (Ph*C*H$_2$), 75.1 (CH-5), 116.9 (=CH-3), 127.5 (2 CH, C_6H_5), 127.7 (2 CH, C_6H_5), 128.3 (CH, C_6H_5), 138.4 (C, C_6H_5), 147.3 (C-2), 153.6 (C=O).

MS (CI, NH_3): *m*/*z* = 392 (MH^+).

Anal. Calcd for $C_{23}H_{37}NO_4$: C, 70.55; H, 9.52; N, 3.58. Found: C, 70.67; H, 9.69; N, 3.54.

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From (–)-sparteine and (*S*)-allyl carbamate [(*S*)-**14**]; $[\alpha]_D$ –20.0 (*c* = 1.20, MeOH).

From (*R*)-allyl carbamate [(*R*)-**14**]/TMEDA; $[\alpha]_D$ –20.0 (*c* = 1.20, MeOH).

***ent*-15**
From (*S*)-allyl carbamate [(*S*)-**14**]/TMEDA; $[\alpha]_D$ +20.0 (*c* = 1.20, MeOH).

(2*Z*,4*S*,5*R*,3*d*,4*d*)-4-[2-(Benzyloxy)ethyl]-2{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxyhept-2-ene (*ent*-d_2-15) and (2*Z*,4*S*,5*R*,3*d*,4*d*)-4-[2-(Benzyloxy)ethyl]-2{[(*N*,*N*-diisopropyl)carbamoyl]oxy}-5-hydroxyhept-2-ene (d_2-15); Optically Active *ent*-d_2-15 from Optically Active Carbamate (*S*)-d_2-14; Typical Procedure
To a solution of TMEDA (0.45 mL, 3 mmol, 2.0 equiv) in anhyd Et_2O–cyclohexane (10 mL/1.0 mL) at –78 °C, under argon, was added *n*-BuLi (1.6 M in hexane, 1.9 mL, 3 mmol, 2.0 equiv). After stirring for 20 min at –78 °C, a solution of the optically active allyl carbamate (*S*)-d_2-**14** (500 mg, 1.5 mmol) in anhyd pentane (3.0 mL), was slowly added. The solution turned pale yellow. After stirring for 1 h at –78 °C, precooled Ti(O*i*-Pr)$_4$ (1.33 mL, 4.5 mmol, 3 equiv) in pentane (5.0 mL) at –78 °C was rapidly added via cannula and the reaction mixture was stirred for 20 min at –78 °C (transmetallation time). Then, freshly distilled propionaldehyde (0.65 mL, 9 mmol, 6 equiv) was added. The mixture was stirred for 2 h at –78 °C and quenched by transferring to a vigorously stirred mixture of aq 3 M HCl (20 mL) and Et_2O (20 mL) at 0 °C. The temperature was allowed to reach 20 °C and the resulting solution was eventually filtered on a pad of Celite to remove titanium salts and extracted with Et_2O. The organic layer was washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane–EtOAc, 70:30), to give the title compound *ent*-d_2-**15** as a pale yellow oil (520 mg, 90% yield, 80% ee).

The same procedure was used with (*R*)-d_2-**14** to give the enantiomeric homoallylic alcohol d_2-**15** with the same enantiomeric excess. The enantiomeric homoallylic alcohol *ent*-d_2-**15** was also obtained with the same enantiomeric excess from the (*S*)-d_2-**14** carbamate using the *n*-BuLi/(–)-sparteine conditions.

Enantiomeric excess were determined by NMR shift experiment with europium salts Eu(hfc)$_3$.

IR (CCl_4): 3395, 1715 cm^{-1}.

^{1}H NMR (400 MHz): δ = 0.94 (t, *J* = 7.4 Hz, 3 H, CH_3-7), 1.24 {d, *J* = 7.2 Hz, 12 H, 4 CH_3, N[CH(C*H*$_3$)$_2$]$_2$}, 1.43 (m, 1 H, H$_a$-6), 1.55 (m, 1 H, H$_a$-1′), 1.57 (m, 1 H, H$_b$-6), 1.83 (dt, *J* = 14, 7 Hz, 1 H, H$_b$-1′), 1.93 (s, 3 H, CH_3-1), 3.40 (dd, *J* = 7.2, 4.3 Hz, 1 H, H-5), 3.45 (m, 1 H, H$_a$-2′), 3.55 (dt, 1 H, H$_b$-2′), 3.82 [br m, 1 H, NC*H*(CH$_3$)$_2$], 4.03 [br m, 1 H, NC*H*(CH$_3$)$_2$], 4.51 (s, 2 H, PhC*H*$_2$), 7.32 (m, 5 H, C_6H_5).

^{13}C NMR (100.6 MHz): δ = 9.6 (CH_3-7), 20.3 {4 CH_3, N[CH(*C*H$_3$)$_2$]$_2$}, 26.9 (CH_3-1), 27.8 (CH_2-1′), 32.2 (CH_2-6), 45.9 and 46.7 {2 CH, N[*C*H(CH$_3$)$_2$]$_2$}, 68.7 (CH_2-2′), 73.1 (Ph*C*H$_2$), 75.1 (CH-5), 127.5 (2 CH, C_6H_5), 127.7 (2 CH, C_6H_5), 128.3 (CH, C_6H_5), 138.4 (C, C_6H_5), 147.3 (C-2), 153.6 (C=O). C-3 and C-4 were not observed.

MS (CI, NH_3): *m*/*z* = 394 (MH^+).

Anal. Calcd for $C_{23}H_{35}D_2NO_2$: C, 70.19; H, 9.99; N, 3.56. Found: C, 70.26; H, 10.17; N, 358.

d_2-15
$[\alpha]_D$ –4.6 (*c* = 2.00, MeOH).

***ent*-d_2-15**
$[\alpha]_D$ +4.2 (*c* = 1.80, MeOH).

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