Michael addition of nitromethane to non-racemic chiral Cr(CO)₃ complexes of ethyl cinnamate derivatives: stereoselective synthesis of (R)-(−)-baclofen

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Abstract

We carried out a highly stereoselective Michael addition (96% de) of nitromethane to enantiomerically pure tricarbonyl(ethyl-4-chloro-2-trimethylsilylcinnamate)chromium(0). This reaction is the key step in the synthesis of (R)-(−)-baclofen, a potent antispastic drug. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

The importance of obtaining enantiomerically pure materials has long been recognized, and there are many and often dramatic examples of biological differences between enantiomer pairs.¹ New methods for producing enantiomerically pure compounds are therefore being actively sought, and widely documented chiral tricarbonyl chromium complexes have emerged as valuable substrates for the stereoselective synthesis of enantiomerically pure organic and organometallic compounds.²

As part of a research programme concerning the study of stereoselective Michael reactions with chiral chromium carbonyl complexes,³ we were interested in using chiral tricarbonyl chromium cinnamate complexes as Michael acceptors.

Some examples of the 1,4-conjugate addition of nucleophiles to chiral tricarbonyl chromium complexes have already been published,⁴ most of which were aimed at studying the stereoselectivity of reactions at a carbon atom in a position remote from the complexed arene moiety. Diastereoselectivities are usually very high (up to 98%) but, to the best of our knowledge, conjugate additions to simple cinnamic ester complexes have not yet been investigated.
2. Results and discussions

We report here the results of the addition of nitromethane\(^5\) to ortho-substituted ethylcinnamate chromium tricarbonyl complexes \(2\text{a,b}\) (Scheme 1). This reaction leads to the \(\gamma\)-nitro esters \(3\text{a,b}\), which are precursors of some important compounds such as pyrrolidines, \(\gamma\)-aminoalcohols and \(\gamma\)-amino acids. The \(\gamma\)-amino-\(\beta\)-aryl butyric acids (lipophilic analogues of GABA) that can be prepared in this way are drugs that have a potent activity on the central nervous system,\(^6\) and one of the most active derivatives is the antispastic \(\gamma\)-amino-\(\beta\)-(\(p\)-chlorophenyl)butyric acid (baclofen) \(7\).\(^7\) Although it is currently sold in racemic form, its pharmacological activity mainly resides in its \((R)\)-enantiomer, and various examples of resolution,\(^8\) chemo-enzymatic\(^9\) or stereoselective\(^{10}\) synthesis have been reported. We have recently published a stereoselective synthesis of \((R)\)-baclofen using chromium carbene chemistry\(^{11}\) and here report a further stereoselective approach to this molecule using chiral chromium tricarbonyl complexes.

In a preliminary experiment aimed at setting up the conditions and evaluating the stereoselection of the reaction, we considered the addition of nitromethane to racemic tricarbonyl(2-methoxy-ethylcinnamate)chromium \(2\text{a}\),\(^{12}\) prepared in good yield from the corresponding benzaldehyde \(1\text{a}\) by means of a Wittig–Horner reaction with triethylphosphono acetate (Scheme 1). The Michael addition of nitromethane was run at room temperature using \(K_2CO_3\) as the base and triethyl benzyl ammonium chloride as the phase transfer catalyst. Nitroester \(3\text{a}\) was obtained in 89% yield and in almost complete diastereoselection, as determined by \(^1H\) NMR.

\[
\begin{align*}
\text{1a,b} & \xrightarrow{(\text{EtO})_3\text{PCH}_2\text{CO}_2\text{Et}} \text{2a,b} & \xrightarrow{\text{CH}_3\text{NO}_2} \text{3a,b} \\
\text{a; } R=\text{OCH}_3, & R'=\text{H} & \text{b; } R=\text{SiMe}_3, & R'=\text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{(R)-6} & \xrightarrow{\text{H}_2, \text{4 atm}} \text{(R)-5} & \xrightarrow{\text{hv, air}} \text{(S)-4} \\
\text{(R)-Baclofen-7}
\end{align*}
\]

Scheme 1.
This encouraging result prompted us to study the application of this reaction to the synthesis of (R)-baclofen 7. As the molecule contains a para-substituted phenyl ring, the corresponding parent ethyl 4-chlorocinnamate complex is not chiral, and so it was necessary to design a chiral complex by introducing an ortho-substituent that was efficient in giving high stereoselection and could be easily removed at the end of the reaction sequence. The trimethylsilyl group, which is a useful site-protecting group in arene complex chemistry, was known to be a suitable substituent for our purpose. We report here a stereoselective synthesis of baclofen that hinges upon the addition of nitromethane to chiral tricarbonyl(ethyl-4-chloro-2-trimethylsilylcinnamate)chromium 2b to give the baclofen precursor nitroester 3b (Scheme 1). The reaction sequence was first run on racemic complex 2b obtained in 88% yield as a trans-isomer from (4-chloro-2-trimethylsilylbenzaldehyde)-Cr(CO)3 1b. The addition of nitromethane to (±)-2b under phase transfer conditions gave nitroester (±)-3b in good yield (92%) and with a high degree of stereoselection (96% de). The treatment of 3b with Bu4NF in CH2Cl2, followed by decomplexation, afforded ethyl 3-(4-chlorophenyl)-4-nitrobutanoate (±)-5. As reported in the literature, catalytic hydrogenation over PtO2 of 5 leads to baclofen 7, whereas the lactam 6 can be obtained by running the reduction with Raney-Ni, and leads to 7 after acid hydrolysis.

Optically active (R)-baclofen was synthesized starting from enantiopure benzaldehyde complex 1b. This complex is known only in the racemic form, but it was resolved by separating the diastereoisomeric semioxamazone derivatives in accordance with a published method. After hydrolysis, both of the enantiomers of 1b ([α]D = +174 and −175.6) were obtained in an 80% average yield. The absolute configuration of complexes (−)-1b and (+)-1b was assigned by correlation with the known configuration of the 2-trimethylsilylbenzaldehyde complex 8. For this purpose, a sample of (+)-1b ([α]D = +174) was dehalogenated by hydrogenation under atmospheric pressure over PtO2, and afforded the (+)-(1S)-2-trimethylsilylbenzaldehydeCr(CO)3 8 as well as the complexed 4-chloro-2-trimethylsilylbenzylalcohol (+)-9 (Scheme 2). On this basis, we were able to assign the (1S)-configuration to the (+)-enantiomer of 1b and the (1R)-configuration to the (−)-enantiomer of 1b.

Both enantiomers of 1 were then transformed into the corresponding (−)-(1R)- and (+)-(1S)-ethylcinnamate complexes 2b. Given the stereochemical model usually operating on such chiral complexes, it was expected that the (R)-enantiomer of baclofen would be generated from the attack of the nitromethane anion on the favourite ‘anti-conformation’ of the double bond in complex (+)-(1S)-1b, as shown in Scheme 3.

On the basis of this hypothesis, the reaction sequence was repeated starting from (+)-(1S)-2b. The addition of nitromethane afforded the nitroester (S,S)-(+)3b in 96% de. Desilylation was run.
using tetrabutylammonium fluoride at room temperature, and the obtained nitroester \((S)-(\pm)\)-4 was then decomplexed to \((R)-(\pm)\)-5 in quantitative yield by means of exposure to air and sunlight.

The enantiomeric purity (96%) of \((\pm)\)-3-(4-chlorophenyl)-4-nitrobutanoate 5, which is known only in the racemic form\(^{16}\), was checked by \(^1\)H NMR using Eu(hfc)\(_3\) as the chiral shift reagent. Hydrogenation of \((\pm)\)-5 at room temperature using Raney-Ni as catalyst gave the lactam \((-)\)-6 in 50% yield, and the corresponding ethyl 3-(4-chlorophenyl)-4-aminobutanoate (35%), which was converted to \((-)\)-6 by means of refluxing in xylene\(^{21}\).

As reported in the literature, the absolute configuration of lactam \((-)\)-6 is \((R)\)^{22}, and \((R)-(\pm)\)-baclofen 7 was obtained from 6 by means of acidic hydrolysis\(^{22}\). This result is in agreement with our hypothesis concerning the stereochemical outcome of the reaction.

### 3. Conclusions

This study shows a further useful application of a chiral arene chromium tricarbonyl complex to the enantioselective synthesis of the biologically important baclofen molecule. Furthermore, this synthetic approach also allows the preparation of the baclofen \((S)\)-enantiomer.

### 4. Experimental

#### 4.1. General

All of the reactions were carried out in a dry nitrogen atmosphere. The reagents and solvents available from commercial sources were used as received unless otherwise noted. Tetrahydrofuran was distilled from a Na/benzophenone ketyl. Column chromatography was performed using Merck silica gel 60 (70–230 mesh). \(^1\)H and \(^{13}\)C NMR spectra were recorded in CDCl\(_3\), using a Bruker AC300 spectrometer. The melting points were measured on a Buchi 510 MP apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1725 FTIR. Optical rotations \([\alpha]_D\) were determined using a Perkin–Elmer 243 polarimeter. Racemic complexes 1a,\(_{13c,19}\) and 2a\(^{12}\) were prepared as reported in the literature.

#### 4.2. Resolution of tricarbonyl(4-chloro-2-trimethylsilylbenzaldehyde)chromium(0) 1b

Racemic benzaldehyde complex 1b was resolved using the Solladié-Cavallo procedure\(^{19}\) as follows: (\(\pm\))1b was refluxed in benzene with a stoichiometric amount of \((S)-(\pm)\)-5-(\(\alpha\)-phenyl-ethyl)semioxamamide and PTSA (10%) to give a mixture of two diastereoisomeric semioxamazones, which were then separated by means of column chromatography using a mixture of

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\[ \text{Scheme 3.} \]
toluene:ethyl acetate (9:1) as eluant. I Diastereoisomer: (80%) $R_f = 0.43$, mp 162–163°C (diisopropylether) $[\alpha]_D = +563$ ($c = 0.12$, CHCl$_3$). IR $\nu_{\max}$/cm$^{-1}$ (CH$_2$Cl$_2$): 1798, 1913, 1686. $^1$H NMR $\delta$ 0.5 (s, 9H, Si(CH$_3$)$_3$), 1.6 (d, 3H, $J = 6.9$ Hz, CH$_3$), 5.1 (m, 1H, CH), 5.45 (d, 1H, $J = 1.9$, arrom), 6.8 (dd, 1H, $J = 7.0$, 1.9 Hz, arrom), 6.1 (d, 1H, $J = 7.0$ Hz, arrom), 7.3 (m, 5H, arrom), 7.7 (bs, 1H, NH), 8.39 (s, 1H, CH= N), 10.3 (bs, 1H, NH). Found: C, 51.41; H, 4.52; N, 7.85; C$_{23}$H$_{24}$ClCrN$_3$O$_5$Si requires: C, 51.35; H, 4.49; N, 7.81. II Diastereoisomer: (83%) $R_f = 0.34$, mp 78–80°C (diisopropylether) $[\alpha]_D = -533$ ($c = 0.12$, CHCl$_3$). IR $\nu_{\max}$/cm$^{-1}$ (CH$_2$Cl$_2$): 1798, 1913, 1789, 1686. $^1$H NMR $\delta$ 0.5 (s, 9H, Si(CH$_3$)$_3$), 1.58 (d, 3H, $J = 6.9$ Hz, CH$_3$), 5.09 (m, 1H, CH), 5.47 (d, 1H, $J = 1.7$ Hz, arrom), 5.68 (dd, 1H, $J = 7.0$, 1.7 Hz, arrom), 6.07 (d, 1H, $J = 7.0$ Hz, arrom), 7.3 (m, 5H, arrom), 7.7 (bs, 1H, NH), 8.42 (s, 1H, CH=N), 10.3 (bs, 1H, NH). Found: C, 51.39; H, 4.44; N, 7.85; C$_{23}$H$_{24}$ClCrN$_3$O$_5$Si requires: C, 51.35; H, 4.49; N, 7.81. Each diastereoisomer was hydrolized by refluxing in benzene with 60% H$_2$SO$_4$ in the presence of an equimolar amount of acetylaceton. After a standard work-up, the corresponding benzaldehyde complex was purified by column chromatography (eluent: petroleum ether:diethyl ether, 3:1): (+)-(1S)-1b (87%) $[\alpha]_D = +177$ ($c = 0.1$, CHCl$_3$), mp 59–61°C (pentane); (−)-(1R)-1b (84%) $[\alpha]_D = -170$ ($c = 0.1$, CHCl$_3$). $^1$H NMR $\delta$ 0.5 (s, 9H, Si(CH$_3$)$_3$), 5.42 (d, 1H, $J = 1.8$ Hz, arrom), 5.65 (dd, 1H, $J = 1.8$, 6.9 Hz, arrom), 5.95 (d, 1H, $J = 6.85$ Hz, arrom), 9.5 (s, 1H, CHO).

4.3. **Tricarbonyl(ethyl-2-methoxycinnamate)chromium(0)** $2a$$^{12}$

Orange solid: (92%) mp 107–109°C (pentane). $^1$H NMR $\delta$ 1.3 (t, 3H, CH$_3$), 3.8 (s, 3H, OCH$_3$), 4.25 (q, 2H, OCH$_2$), 4.92 (dd, 1H, $J = 6.3$, 6.4 Hz arrom), 5.07 (d, 1H, $J = 6.7$ Hz arrom), 5.63 (dd, 1H, $J = 6.4$, 6.7 Hz, arrom), 5.85 (dd, 1H, $J = 6.3$ Hz, arrom), 6.28 (d, 1H, $J = 16.1$ Hz, =CH), 7.64 (d, 1H, $J = 16.1$ Hz, =CH). $^{13}$C NMR $\delta$ 0, 14, 56, 60.7, 73.2, 84.6, 89.1, 93.34, 94.2, 119, 137.2, 142.3, 167, 232. (+)-(1S)-2a (86%) $[\alpha]_D = +611$ ($c = 0.21$, CHCl$_3$).

4.4. **Tricarbonyl(ethyl-4-chloro-2-trimethylsilylcinnamate)chromium(0)** $2b$

Lithium hexamethyldisilylamide (0.8 mL of a 1 M solution in THF) was added at room temperature to a stirred solution of diethylphosphonate acetate (170 mg, 0.76 mmol) in THF (5mL). This solution was added dropwise at 0°C to complex 1 (250 mg, 0.8 mmol) dissolved in THF (3 mL). After stirring for 1 h at room temperature, the mixture was diluted with an aqueous solution of NH$_4$Cl (10 mL) and extracted with Et$_2$O (3×10 mL). The combined organic phases were washed with water (15 mL), dried (Na$_2$SO$_4$), filtered and evaporated to give 300 mg of a dark orange solid. Column chromatography gave 280 mg (88%) of $2b$ and 25 mg (10%) of the corresponding desilylated tricarbonyl[(ethyl-4-chlorocinnamate)chromium] $2c$ (see above). Compound (+)2b: $R_f = 0.31$, mp 73–74°C (pentane). Found: C, 49.98; H, 4.64; C$_{17}$H$_{19}$ClCrO$_5$Si requires: C, 48.75; H, 4.57. IR $\nu_{\max}$/cm$^{-1}$ (nujol): 1798, 1909, 1713, 1285. $^1$H NMR $\delta$ 0.5 (s, 9H, Si(CH$_3$)$_3$), 1.3 (t, 3H, CH$_3$), 4.2 (q, 2H, OCH$_2$), 5.49 (d, 1H, $J = 1.9$ Hz, arrom), 5.52 (d, 1H, $J = 6.9$ Hz, arrom), 5.68 (dd, 1H, $J = 6.9$, 1.9 Hz, arrom), 6.2 (d, 1H, $J = 15.6$ Hz, =CH), 7.5 (d, 1H, $J = 15.6$ Hz, =CH). $^{13}$C NMR $\delta$ 0, 14, 61, 89, 93, 97, 102, 103, 110, 122, 142, 165, 230. Compound (−)2b (85%) mp 62–63°C, $[\alpha]_D = +645$ ($c = 0.1$, CHCl$_3$). Compound (−)2b (83%) $[\alpha]_D = -661$ ($c = 0.1$, CHCl$_3$). Compound 2c: $R_f = 0.17$, mp 139°C (pentane). Found: C, 48.46; H, 3.23; C$_{16}$H$_{19}$ClCrO$_5$ requires: C, 48.50; H, 3.20. IR $\nu_{\max}$/cm$^{-1}$ (nujol): 1983, 1918, 1712. $^1$H NMR $\delta$ 1.3 (t, 3H, CH$_3$), 4.25 (q, 2H, OCH$_2$), 5.4 (d, 2H, $J = 7.5$ Hz, arrom), 5.6 (d, 2H, $J = 7.5$ Hz, arrom), 6.2 (d, 1H, $J = 16.8$ Hz, =CH), 7.1 (d, 1H, $J = 16.8$ Hz, CH=).
4.5. Tricarbonyl[ethyl 3-(2-methoxyphenyl)-4-nitrobutanoate]chromium(0) 3a

K$_2$CO$_3$ (170 mg, 1.2 mmol) and TEBA (15 mg) were added to a solution of complex 2a (200 mg, 0.58 mmol) in CH$_3$NO$_2$ (12 mL). The mixture was vigorously stirred at room temperature for 1 h and its colour changed from orange to yellow. Brine (30 mL) was added, and the mixture was then extracted using Et$_2$O (4×20 mL). After washing with H$_2$O (25 mL), the combined organic layers were dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was taken up with diethyl ether, charcoal was added and the solution was filtered over a pad of Celite$^*$ to give 210 mg of 3a (89%) as a yellow oil. IR $\nu$$_{\max}$/cm$^{-1}$ (nujol): 1958, 1870, 1729, 1554, 1376. $^1$H NMR $\delta$ 1.3 (t, 3H, CH$_3$), 2.8–2.95 (m, 2H, CH$_2$CO), 3.8 (s, 3H, OCH$_3$), 3.9–4.0 (m, 1H, CH), 4.2–4.25 (m, 2H, CH$_2$O), 4.8 (d, 2H, $J$= 6.5 Hz, CH$_2$NO$_2$), 4.87 (dd, 1H, $J$= 6.2, 6.3 Hz, arom), 5.05 (d, 1H, $J$= 6.65 Hz, arom), 5.56–5.62 (m, 2H, arom). Compound 3a was dissolved into CH$_2$Cl$_2$ (10 mL) and decomplexed by exposure to air and sunlight. After the evaporation of the solvent, the residue was taken up with Et$_2$O (10 mL) and filtered over Celite$^*$ to give ethyl 3-(2-methoxyphenyl)-4-nitrobutanoate 3d as a colourless oil in 95% yield. IR (neat): $\nu$$_{\max}$/cm$^{-1}$ (nujol) 1735, 1560, 1350. $^1$H NMR 1.25 (t, 3H, CH$_3$), 2.92 (d, 2H, $J$= 7.3 Hz, CH$_2$CO), 3.8 (s, 3H, OCH$_3$), 4.1 (q, 2H, CH$_2$O), 4.25 (dd, 2H, $J$= 7.4, 7.1 Hz CH$_2$NO$_2$), 4.8–4.9 (m, 1H, CH), 6.9–7.0 (m, 2H, arom), 7.2–7.35 (m, 2H, arom).

4.6. Tricarbonyl[ethyl 3-(4-chloro-2-trimethylsilylphenyl)-4-nitrobutanoate]chromium(0) 3b

A solution of complex 2b (200 mg, 0.48 mmol) in nitromethane (2 mL) was dropped into a suspension of K$_2$CO$_3$ (90 mg, 0.65 mmol) and TEBA (15 mg) in CH$_3$NO$_2$ (10 mL). The mixture was vigorously stirred at room temperature for 3 h. Brine (30 mL) was added, and the yellow mixture extracted using Et$_2$O (4×20 mL). After washing with H$_2$O (30 mL), the combined organic layers were dried (Na$_2$SO$_4$) and evaporated under reduced pressure to give 230 mg of a yellow solid. Column chromatography (eluent: light petroleum:diethyl ether, 4:1) ordered 210 mg (92%) of 3b and 10 mg (5%) of unreacted 2b. Compound (+)-3b: mp 99–100°C (pentane). Found: C, 45.33; H, 4.60; N, 2.95; C$_{18}$H$_{22}$ClCrNO$_7$Si requires: C, 45.05; H, 4.62; N, 2.92. IR $\nu$$_{\max}$/cm$^{-1}$ (nujol): 1976, 1908, 1732, 1558, 1388. $^1$H NMR $\delta$ 0.5 (s, 9H, Si(CH$_3$)$_3$), 1.3 (t, 3H, CH$_3$), 2.8–2.95 (m, 2H, CH$_2$CO), 3.7 (s, 3H, OCH$_3$), 4.1 (q, 2H, CH$_2$O), 3.8–4.0 (m, 1H, CH), 4.25 (dd, 2H, $J$= 7.4, 7.1 Hz CH$_2$NO$_2$), 4.8–4.9 (m, 1H, CH), 6.9–7.0 (m, 2H, arom), 7.2–7.35 (m, 2H, arom). $^{13}$C NMR $\delta$ 14.1, 35.8, 36.8, 55.4, 60.7, 77.8, 110.1, 120.8, 125.9, 129.1, 129.4, 157.2, 170.3; $m/z$: 480, 452 (–CO), 424 (–2CO), 419 (–CH$_2$NO$_2$), 396 (–3CO), 344 (–Cr(CO)$_3$). Compound (S,S)-(+)–3b: $[\alpha]_D$ = +54 ($c$ = 0.23, CHCl$_3$), mp 60–62°C. Compound (R,R)-(−)–3b: $[\alpha]_D$ = −59 ($c$ = 0.3, CHCl$_3$).

4.7. Tricarbonyl[ethyl 3-(4-chlorophenyl)-4-nitrobutanoate]chromium(0) 4

Tetrabutylammonium fluoride trihydrate (170 mg, 0.56 mmol) was added to a CH$_2$Cl$_2$ (10 mL) solution of 3b (300 mg, 0.6 mmol), and the mixture was stirred for 30 min at room temperature. Brine (20 mL) was added, and the mixture was extracted using CH$_2$Cl$_2$ (4×15 mL). After washing with H$_2$O (15 mL), the combined organic layers were dried (Na$_2$SO$_4$) and evaporated under reduced pressure. The residue was taken up with Et$_2$O and filtered over Celite$^*$. Column chromatography (eluent: light petroleum:diethyl ether, 1:1) gave 200 mg (85%) of 4 as a yellow solid. Compound (+)-4: mp 66–68°C (pentane). Found: C, 44.23; H, 3.42; N, 3.41; C$_{13}$H$_{14}$ClCrNO$_7$.
requires: C, 44.19; H, 4.46; N, 3.43. IR νmax/cm⁻¹ (nujol): 1958, 1909, 1876, 1650, 1549. ¹H NMR δ 1.25 (t, 3H, CH₃), 2.72 (dd, 2H, J=CH₂CO), 3.5 (m, 1H, CH), 4.17 (q, 2H, CH₂O), 4.6 (dd, 1H, J=CH₂NO₂), 4.75 (dd, 1H, J=CH₂NO₂), 5.37–5.42 (m, 4H, arom). Compound (S)-(+)-4: [α]D = +15.2 (c = 0.4, CHCl₃), mp 75–76°C. Compound (R)-(−)-4: [α]D = −17 (c = 0.3, CHCl₃).

4.8. Ethyl 3-(4-chlorophenyl)-4-nitrobutanoate 5

Complex 4 (200 mg, 0.49 mmol) was dissolved in CH₂Cl₂ (10 mL) and decomposed by exposure to air and sunlight. After the evaporation of the solvent, the residue was taken up with Et₂O (10 mL), charcoal was added and the solution was filtered over Celite® to give 5 as a colourless oil in 95% yield. Compound 5 was identified by comparison with an authentic sample.¹⁶ Compound (R)-(−)-5: [α]D = +3.9 (c = 0.1, CHCl₃).

4.9. (R)-(−)-4-(4-Chlorophenyl)pyrrolidin-2-one 6

Nitroester 5 (0.2 g, 0.74 mmol) was dissolved in 10 mL of EtOH, and after the addition of 0.05 g of methanol–wet Raney-Ni, the mixture was hydrogenated for 8 h at room temperature under 4 atm of H₂ pressure. The mixture was suction filtered (taking the necessary precautions for handling pyrophoric catalysts), and the residue on the filter was washed several times with ethanol. The solvent was evaporated and the residue, purified by column chromatography (AcOEt), gave 65 mg (30%) of unreduced 5 and 90 mg (61%) of lactam (R)-6: [α]D = −38.3 (c = 0.5, EtOH) (lit.²² [α]D = −39, c = 1, EtOH). Acid hydrolysis of (−)-6 afforded (R)-baclofen as hydrochloride.

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14. De was determined by $^1$H NMR on the crude reaction mixture; diastereoisomeric purity can be increased up to 98% by crystallization.

15. Davies for 2-trimethylsilylebenzaldehyde,12a,b in which the nucleophilic attack takes place on the opposite face because of the chelation between the C=O and the trimethylsilyl group.