HETEROCYCLES, Vol. 59, No. 2, 2003, pp. 785 - 791, Received, 10th October, 2002

A DIASTEREOCONTROLLED ROUTE TO (*R*)-(–)-BACLOFEN USING A CYCLOPENTANOID CHIRAL BUILDING BLOCK

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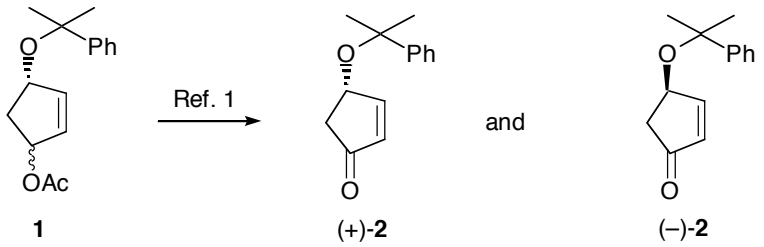
Abstract – A diastereoselective route to the key intermediate lactone leading to a $GABA_B$ receptor agonist (*R*)-(–)-baclofen has been developed starting from (+)-4-cumyloxycyclopent-2-en-1-one *via* the 4-arylcyclopentenone intermediate.

We have recently developed a preparation of enantiopure 4-cumyloxycyclopent-2-en-1-one (**2**) in both enantiomeric forms from a diastereomeric mixture of the 3,5-dioxygenated cyclopentene (**1**) by employing enzymatic kinetic resolution as the key step[1] (Scheme 1).

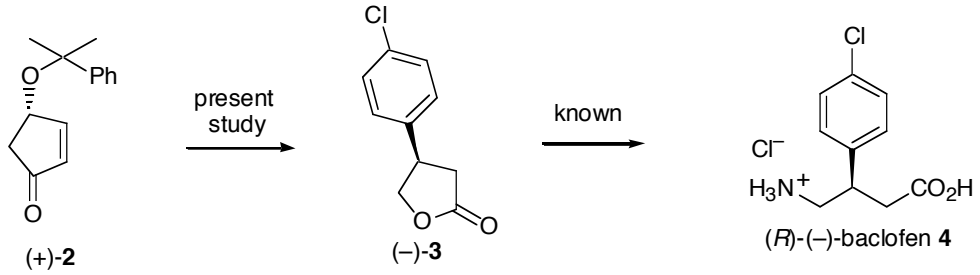


1 (+)-**2** (–)-**2**

Scheme 1

Owing to the 4-cumyloxy functionality, the chiral enone (**2**) allowed a cuprate-mediated 1,4-addition in a highly diastereoselective manner to give exclusively the *trans*-3,4-disubstituted cyclopentenones of which stereochemistry was proved by the synthesis of stereo-defined natural products having a □-lactone chromophore.[2] Moreover, the observed stereochemical behavior has been reflected in the diastereocontrolled synthesis of a variety of natural products.[3] Since the *trans*-3,4-disubstituted cyclopentanones generated from the cyclopentene precursor (**2**) possess a □-cumyloxy functionality, it is readily assumed that the cyclopentanones afford the corresponding 4-substituted cyclopentenones by elimination of the □-alkoxy functionality if racemization does not occur. We therefore sought the optimal

conditions for the elimination of the -alkoxy functionality without suffering racemization and found that the expected reaction did take place keeping original chiral integrity when the 4-substituent is an aryl.[4] We show here an example of the diastereoselective synthesis of the enantiopure 4-aryl enone ((+)-**6**) leading to the key intermediate lactone ((–)-**3**) for the synthesis of a $GABA_B$ receptor agonist (*R*)-(–)-baclofen (**4**)[5,6] (Scheme 2).

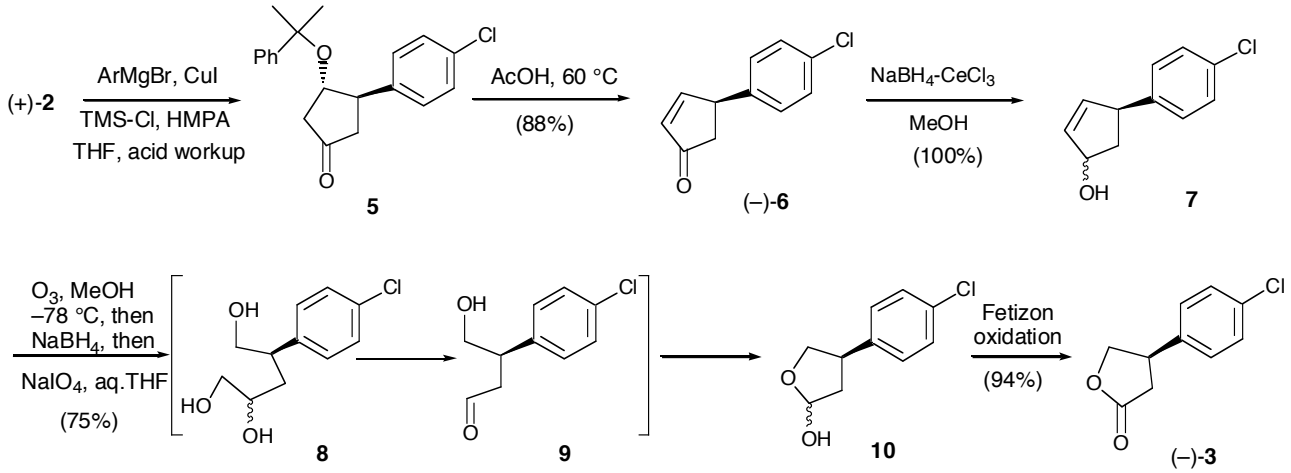


Scheme 2

The 1,4-addition of the cuprate to the enone ((+)-**2**) proceeded smoothly under the Kuwajima conditions.[7] Thus, on exposure to the cuprate generated *in situ* from 4-chlorophenylmagnesium bromide[6c] in THF containing hexamethylphosphoric triamide (HMPA) in the presence of copper (I) iodide and chlorotrimethylsilane, the enantiopure enone ((+)-**2**) afforded the *trans*-3,4-disubstituted cyclopentanone ((+)-**5**) selectively as the single diastereomer after hydrolysis of the silyl enolate product under acidic conditions. After extensive experimentation under both acidic and basic conditions, it was found that the -elimination took place without causing any racemization under acidic conditions using acetic acid. Thus, on stirring in acetic acid at 60 °C for 20 h, the 3,4-disubstituted cyclopentanone ((+)-**5**) afforded the enantiopure 4-arylcyclopent-2-en-1-one ((–)-**6**) in excellent yield. The present transformation implies the replacement of a 4-cumyloxy functionality on the cyclopentanone ((+)-**2**) by an aryl functionality with retention of the stereochemistry in a formal sense. The overall yield of the 4-arylcyclopentenone ((–)-**6**) from the 4-cumyloxycyclopentenone ((+)-**2**) was 79% in two steps.

In order to confirm the stereochemistry as well as to find utilization of the product, the enone ((+)-**6**) was transformed into the known lactone ((–)-**3**) from which ((*R*)-(–)-baclofen **4**) has been obtained in four steps.[6d] Thus, the enone ((–)-**6**) was first reduced with sodium borohydride in the presence of cerium (III) chloride[8] to give the cyclopentenol (**7**) as a 3:1 mixture of two epimers. It is interesting to note that the 4-aryl substituent in the cyclopentenone ((–)-**6**) did not exhibit a significant diastereocontrolled effect under these reduction conditions since we have observed high diastereoselectivity (>99 de) in the reaction of the cyclopentanone (**2**) having a 4-cumyloxy functionality under the same conditions.[1,3] For

the present purpose, the reduction product without separation was sequentially ozonized, reduced with sodium borohydride and cleaved with sodium periodate in the same flask to afford the hemiacetal mixture (**10**) as a 1.7:1 mixture *via* the transient intermediates, the triol (**8**) and the hydroxy aldehyde (**9**). Finally, the hemiacetal mixture **10**) was refluxed with Fetizon reagent[9] in toluene to give the lactone ((*S*)-(–)-**3**) of which spectral and physical data were identical in all respects with those reported.[6d] The overall yield of the lactone ((*S*)-(–)-**3**) from the arylenone ((–)-**6**) was 71% in three steps, thus, in 56% from the starting 4-cumyloxycyclohexenone ((+)-**2**) in five steps (Scheme 3).



Scheme 3

In conclusion, we have succeeded in replacing the 4-cumyloxy functionality on cyclopentanone by an aryl functionality retaining the original chiral integrity in a formal sense. The stereochemistry observed has been confirmed by developing an alternative route to a $GABA_B$ receptor (*R*)-(–)-baclofen.

EXPERIMENTAL

The melting points were determined on a Yanagimoto hot-stage and are uncorrected. IR spectra were recorded on a JASCO-IR 700 spectrophotometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in $CDCl_3$ on a Varian Gemini-2000 (300 MHz) spectrometer. Enantiomeric purities were determined on a Gilson Model-307 instrument equipped with a column with a chiral stationary phase.

(3*S*,4*R*)-3-(4-Chlorophenyl)-4-cumylooxycyclopentan-1-one ((+)-5): To a stirred solution of CuI (660 mg, 3.47 mmol) and HMPA (3.3 mL) in THF (10 mL) was added a solution of 4-chlorophenylmagnesium bromide in THF (1 M in THF, 6.9 mL, 6.9 mmol) followed by a solution of chlorotrimethylsilane (TMS-Cl) in THF (0.67 mL, 4.62 mmol in THF 3.3 mL) at –78 °C and, after

stirring for 20 min at the same temperature, the temperature was raised to 0 °C and, after 1 min, cooled again to –78 °C and the stirring was continued for 30 min at the same temperature. To this mixture was then added a mixture of the enone (+)-(**2**)) (500 mg, 2.31 mmol) and trimethylchlorosilane (0.67 mL, 4.62 mmol) in THF 3.3 mL at the same temperature. After stirring at the same temperature for 30 min, the reaction was quenched by addition of 10% diluted hydrochloric acid and extracted with ether. The extract was washed successively with brine and 5% aqueous $NaHCO_3$, dried ($MgSO_4$), evaporated under reduced pressure, and the residue was chromatographed (SiO_2, elution with AcOEt-hexane 1:10 v/v) to give the cyclopentanone ((+)-**5**) (629 mg, 89.6%) as colorless needles: mp 46-48 °C (from hexane), $[\alpha]_D^{29}$ +45.5° (*c* 0.95, $CHCl_3$). IR (film): ν = 1744 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.34 (s, 3H), 1.47 (s, 3H), 2.22-2.31 (m, 2H), 2.46 (dd,1H, *J* = 18.3, 6.5 Hz), 2.72 (ddd,1H, *J* = 18.8, 10.0, 1.0 Hz), 3.32 (td, 1H, *J* = 9.2, 7.1 Hz), 3.82 (dd, 1H, *J* = 14.8, 7.4 Hz), 6.99 – 7.16 (m, 9H). ^{13}C NMR ($CDCl_3$): δ = 27.62, 28.93, 31.42, 43.73, 47.06, 49.07, 76.45, 116.60, 124.26, 125.88, 126.46, 127.00, 127.85, 128.02, 128.46, 128.78, 129.21, 132.44, 139.26, 144.98, 214.59. MS: m/z = 328 (M^+). HRMS: Calcd for $C_{20}H_{21}O_2Cl$ (M^+) = 328.1230. Found: 328.1278.

(4*R*)-4-(4-Chlorophenyl)cyclopent-2-en-1-one ((–)-6): A solution of the ketone ((+)-**5**) (679 mg, 2.07 mmol) in AcOH (12 mL) was stirred at 60 °C for 20 h. After cooling, the mixture was diluted with AcOEt and the solution was washed successively with brine, saturated aqueous NH_4Cl and brine, and dried on $MgSO_4$. The solution was evaporated under reduced pressure and and the residue was chromatographed (SiO_2, elution with AcOEt-hexane 1:15 v/v) to give the cyclopentenone ((–)-**6**) (350 mg, 88.2%) as colorless needles: mp 41-42 °C (from hexane), $[\alpha]_D^{29}$ –308° (*c* 1.37, $CHCl_3$). IR (film): ν = 1711 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 2.28 (dd, 1H, *J* = 18.9, 2.5 Hz), 6.34 (dd,1H, *J* = 7.8, 2.1 Hz), 7.09 (td, 1H, *J* = 8.5, 2.1 Hz), 7.27 – 7.66 (m, 4H). ^{13}C NMR ($CDCl_3$): δ = 43.83, 45.99, 128.60, 129.25, 133.17, 134.49, 140.06, 166.07, 209.55. MS: m/z = 192 (M^+). HRMS: Calcd for $C_{11}H_9OCl$ (M^+) = 192.0342. Found: 192.0366. Optical purity = >99%ee by HPLC (CHIRALCEL OJ, elution with *i*-PrOH-hexane 1:19 v/v).

4-(4-Chlorophenyl)cyclopent-2-en-1-ol (7): To a stirred solution of the enone (–)-(**6**) (100 mg, 0.52 mmol) and $CeCl_3$-$7H_2O$ (214 mg, 0.57 mmol) in MeOH (2.6 mL) was added $NaBH_4$ (20 mg, 0.52 mmol) at 0 °C. After stirring at the same temperature for 30 min, the reaction was quenched by addition of acetone and the mixture was extracted with AcOEt. The extract was washed with brine, dried ($MgSO_4$), evaporated under reduced pressure, and and the residue was chromatographed (SiO_2, elution with AcOEt-hexane 1:8 v/v) to give the cyclopentenol (**7**) (101 mg, 100%) as colorless crystals: mp 83-85 °C (from hexane). IR (film): ν = 3287 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.53 (dt, 0.75H, *J* = 13.7, 5.6 Hz), 1.73 –

1.83 (m, 1H), 2.04 (ddd, 0.25H, *J* = 14.3, 6.9, 5.6 Hz), 2.28 (ddd, 0.25H, *J* = 14.2, 8.0, 2.7 Hz), 2.83 (dt, 0.75H, *J* = 15.2, 6.9 Hz), 3.76 (m, 0.75 H), 4.11 (ddd, 0.25 H, *J* = 7.7, 6.9, 5.9, 2.1 Hz), 4.93 (t,0.75H, *J* = 5.5 Hz), 5.03 – 5.05 (m, 0.25H), 5.91 (dt, 0.75H, *J* = 5.5, 1.5 Hz), 5.97 – 6.06 (m, 1.5 H), 7.04 – 7.28 (m, 4H). MS: m/z = 194 (M^+). HRMS: Calcd for $C_{11}H_{11}OCl$ (M^+) = 194.0498. Found: 194.0468.

4-(4-Chlorophenyl)-2-hydroxy-*2H*-2,3,4,5-tetrahydrofuran (**10**)**:** To a stirred solution of the cyclopentenol (**7**) (211 mg, 1.09 mmol) in MeOH (11 mL) was introduced ozone at –78 °C for 10 min. After evacuation of the ozone by bubbling argon, to this mixture was added $NaBH_4$ (412 mg, 10.9 mmol) at the same temperature and, after 30 min, the reaction was quenched by addition of acetone and the mixture was diluted with AcOEt. The solution was washed with brine, dried ($MgSO_4$), extracted with AcOEt, and evaporated under reduced pressure to leave the crude triol (**8**).

The crude triol (**8**) was dissolved in THF (5.5 mL) and the solution was stirred with aqueous $NaIO_4$ (1.17 g, 5.45 mmol in H_2O 5.5 mL) at rt for 2 h. The mixture was extracted with AcOEt and the extract was washed successively with brine and saturated $NaHCO_3$, dried ($MgSO_4$) and the residue was chromatographed (SiO_2, elution with AcOEt-hexane 1:6 v/v) to give the lactol (**10**) (163 mg, 75.3%) as colorless crystals: mp 47-49 °C (from hexane). IR (film): □ = 3346 cm^{-1}. ^1H NMR ($CDCl_3$): □ = 1.95 (ddd, 0.4H, *J* = 13.6, 10.7, 3.0 Hz), 1.73 – 1.83 (m, 1H), 2.07 (dddd, 0.6H, *J* = 12.9, 9.0, 4.9, 1.1 Hz), 2.35 (dd, 0.6H, *J* = 12.9, 7.4 Hz), 2.63 (ddd, 0.4H, *J* = 13.9, 9.4, 5.0 Hz), 3.36 – 3.93 (m, 3H), 4.20 (t, 0.4 H, *J* = 8.1 Hz), 4.42 (t,0.6H, *J* = 7.8 Hz), 5.85 (dt, 1H, *J* = 8.0, 2.7 Hz), 7.15 – 7.31 (m, 4H). MS: m/z = 198 (M^+). HRMS: Calcd for $C_{10}H_{11}O_2Cl$ (M^+) = 198.0448. Found: 198.0430.

4-(4-Chlorophenyl)tetrahydrofuran-2-one (**(–)-3**)**:** A suspension of the lactol (**10**) (68 mg, 0.34 mmol) and Fetizon reagent (375 mg, 0.68 mmol) in toluene (3.4 mL) was refluxed for 1 h. After cooling, the suspension was filtered through a Celite pad and the filtrate was evaporated under reduced pressure and the residue was chromatographed (SiO_2, elution with AcOEt-hexane 1:5 v/v) to give the lactone ((–)-**3**) (26 mg, 93.6%) as colorless needles: mp 73-75 °C (from hexane), $[□]_D^{29}$ –51.8° (*c* 1.38, $CHCl_3$){lit.[6k]: $[□]_D^{25}$ –51° (*c* 0.5, $CHCl_3$)}. IR (film): □ = 1774 cm^{-1}. ^1H NMR ($CDCl_3$): □ = 2.63 (dd, 1H, *J* = 17.4, 8.8 Hz), 2.94 (dd, 1H, *J* = 17.6, 8.8 Hz), 3.77 (q, 1H, *J* = 8.2 Hz), 4.24 (dd, 1 H, *J* = 9.1, 7.7 Hz), 4.66 (dd, 1H, *J* = 9.1, 7.7 Hz), 4.66 (dd, 1H, *J* = 9.2, 7.8 Hz), 7.25 – 7.27 (m, 4H). ^{13}C NMR ($CDCl_3$): □ = 35.27, 40.15, 73.49, 128.04, 129.06, 133.22, 137.99, 170.06. MS: m/z = 196 (M^+). MS: m/z = 198 (M^+). HRMS: Calcd for $C_{10}H_9O_2Cl$ (M^+) = 196.0291. Found: 1968.0274. The spectral data were identical with those reported.[6r]

ACKNOWLEDGEMENTS

The authors thank the Ministry of Education, Culture, Sports, Science and Technology, Japan for support of this research. We also thank Professor Yoshiharu Iwabuchi, Pharmaceutical Institute, Tohoku University, for his kind suggestion.

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