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Efficient resolution of some monoprotected derivatives of Corey lactone

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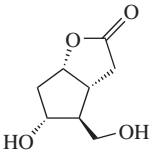
Racemic monoprotected at primary hydroxy group Corey lactones were resolved using (1*S*,2*R*,5*R*)-6,6-dimethyl-4-oxo-3-oxabicyclo-[3.1.0]hexan-2-ol as a chiral auxiliary reagent of hemiacylal chemotype.

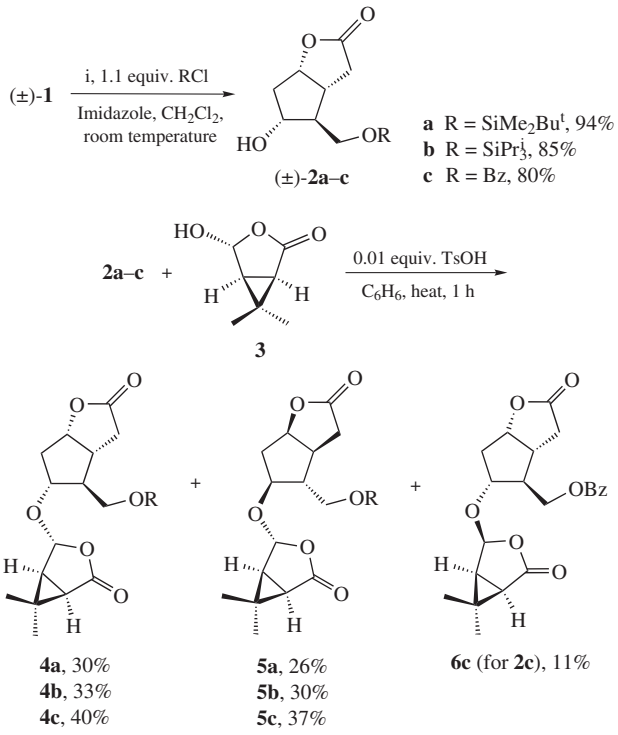
(–)-Lactone diol **1** (the Corey lactone) and its monoprotected derivatives such as **2** are widely used as key synthons in the non-cuprate 'linear' synthesis of natural prostaglandins and their analogues.[1,2] The syntheses of (±)-**1**,**2** have already been reported.[3–6] The main problem in these syntheses is producing the corresponding enantiopure form. The known procedures involve the use of enzymatic methods,[7] the separation of suitable diastereomeric derivatives of (±)-**1**[8] and resolution of the (±)-**1** precursors.[9] However, each of these methods suffers from shortcomings: the necessity of the tedious search for appropriate enzymes, of the repeated crystallization of diastereomeric derivatives and so on.



(–)-**1**

In this communication, we report a simple and practical method for the production of both enantiomers of (±)-**2** *via* an easy separation of their diastereomeric derivatives obtained with the readily available homochiral hemiacylal **3**[10] (Scheme 1). It seemed reasonable to facilitate the resolution by firstly transforming the primary hydroxy group in compound **1** to obtain derivatives **2a–c** with bulky silane or benzoate protective groups followed by chiral derivatization of the secondary hydroxyl. Derivatives **2a–c** were easily prepared by selective reaction of (±)-**1** with the corresponding RCl under standard conditions.[11,†]

The TsOH-catalyzed reaction of alcohols **2a–c** with hemiacylal **3** proceeded equally well in refluxing benzene with azeotropic removal of water. Note that catalysis with camphorsulfonic acid



Scheme 1

† *General protocol for silane derivatives* **2a**,**b**. Imidazole (0.87 g, 12.78 mmol) and chlorosilane R_3SiCl (6.39 mmol) were added (in case of **2b**, 15 mg of DMAP were also added) to a stirred solution of (±)-**1** (1.0 g, 5.81 mmol) in 10 ml of anhydrous CH_2Cl_2 under argon at 0 °C. Stirring at room temperature was continued overnight. The imidazole hydrochloride was removed by filtration through a short pad of Celite and washed with CH_2Cl_2 (2×5 ml). The combined filtrates were washed with water and aqueous $NaHCO_3$ (2×3 ml), brine and dried. Removal of the solvent under reduced pressure afforded the required silanes.

General protocol for **2c**. A solution of benzoyl chloride (6.39 mmol) in 5 ml of pyridine was added to a stirred solution of (±)-**1** (1.0 g, 5.81 mmol) in 10 ml of anhydrous pyridine under argon at 0 °C. The reaction mixture was stirred at room temperature for 24 h. After removal of pyridine and pyridine hydrochloride, the crude product was purified by silica gel chromatography.

General protocol for acylales **4**–**6**. A solution of (±)-**2a**,**b** (1.0 mmol), **3** (1.05 mmol) and anhydrous TsOH (0.01 mmol) in dry benzene (20 ml) was stirred and refluxed for 1 h with continuous removal of water with a Dean–Stark trap. The solution was concentrated under reduced pressure, and the residue was diluted with CH_2Cl_2 (5 ml) and washed with water (2×3 ml) and brine, and then dried over Na_2SO_4. Removal of the solvent under reduced pressure produced oil, which was fractionated by column chromatography.

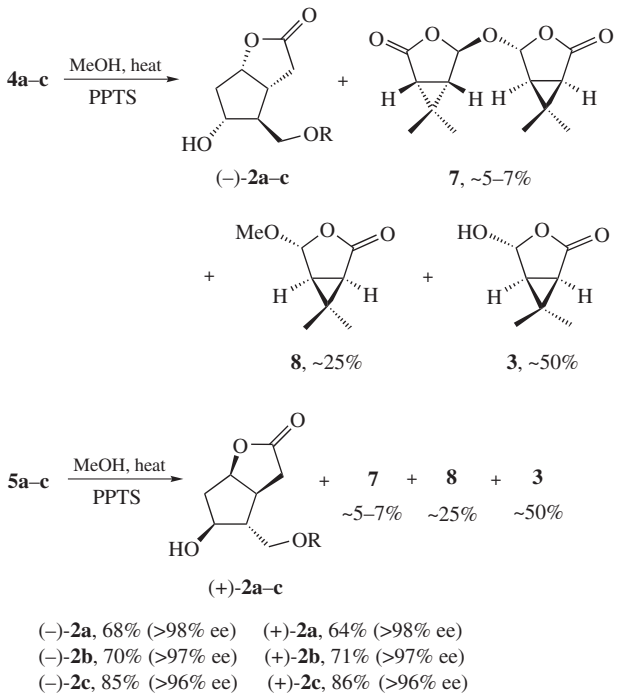
General protocol for enantiomeric silanes **2a**,**b** *and benzoates* **2c**. A solution of a diastereomer **4** or **5** (0.5 mmol) and PPTS (5 mg, 0.02 mmol) in 10 ml of MeOH was stirred at 60 °C for 1 h. The solvent was evaporated *in vacuo*. The residue was dissolved in water (10 ml) and extracted with CH_2Cl_2 (3×5 ml). The combined organic phases were washed with water and brine. Removal of the solvent under reduced pressure and column chromatography of the residue on silica gel afforded the required products as well as recovered chiral auxiliary **3** (~50%), dimer **7** (~5–7%) and methyl acetal **8** (~25%). The spectral features of the enantiomeric **2a–c** were identical with spectral features of the corresponding racemic mixtures.

For characteristics of compounds synthesized, see Online Supplementary Materials.

(CSA) led to intense hydrolysis of the silane protective group in the case of **2a**, whereas pyridinium-*p*-toluenesulfonate (PPTS) was not effective.

Diastereomeric products **4a–c** and **5a–c** were formed in the reaction in nearly equal quantities in 56–77% overall yields.[†] Epimerization of chiral centre in reagent **3** occurred to a negligible extent only in the case of **2c**, when anomeric product **6c** was isolated (although in insignificant amounts) along with the major products **4c** and **5c**. The configuration of **6c** follows from the doublet (*J* 4.2 Hz) character of the anomeric H-2′ signal in the ^{1}H NMR spectrum, whereas compounds **4** and **5** display the corresponding signal as a singlet.

Diastereomeric pairs of **4a–c** and **5a–c** differed significantly in their mobility during chromatography on silica gel (ΔR_f = = 0.04–0.10) and could be easily thus separated. The regeneration of (–)-**2a–c** and their corresponding (+)-enantiomers from the individual diastereomers **4a–c** and **5a–c** was achieved by short heating with a catalytic amount of PPTS in MeOH (Scheme 2). The chiral auxiliary **3** was recovered in 50% yield along with dimer **7** (~5–7%) and methyl derivative **8** (~25%) (*cf.* ref. 18). Compounds **7** and **8** can be transformed into lactol **3** by acidic hydrolysis.



(–)-**2a**, 68% (>98% ee) (+)-**2a**, 64% (>98% ee)
(–)-**2b**, 70% (>97% ee) (+)-**2b**, 71% (>97% ee)
(–)-**2c**, 85% (>96% ee) (+)-**2c**, 86% (>96% ee)

Scheme 2

In summary, we have elaborated a three-step protocol that produces enantiomers of the Corey lactone derivatives **2a–c** from racemic lactone (±)-**1** in overall yields 20–25%. This protocol provides an additional example of the hemiacylal **3** [(–)-**3** or (+)-**3**] efficacy as a reagent for the resolution of racemic alcohols, in addition to the published resolutions of alletrolone,[13] 4-hydroxy-2-cyclopenten-1-one,[14] lineatine,[15] 2-allyl-4-hydroxycyclopentenone[16] *etc*.[17] Taking into consideration the importance and prevalence of the Corey strategy in the prostaglandin synthesis, we hope the protocol described above could find an application in the chemistry of prostaglandins and other cyclopentanoids as well.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2012.05.002.

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