Preparation of a Promising Cyclobutanone Chiral Building Block: Its Stereochemistry and Utilization

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Abstract: A cyclobutanone possessing a bicyclo[2.2.1]heptene framework {*endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one} has been prepared in both enantiomeric forms employing lipase-mediated kinetic resolution as the key step. To determine the absolute configuration, as well as to demonstrate the synthetic potential, both enantiomers of the cyclobutanone obtained have been transformed enantioconvergently into the key intermediate of the sesquiterpene (+)-β-santalene and the iridoid monoterpene (–)-boschnialactone.

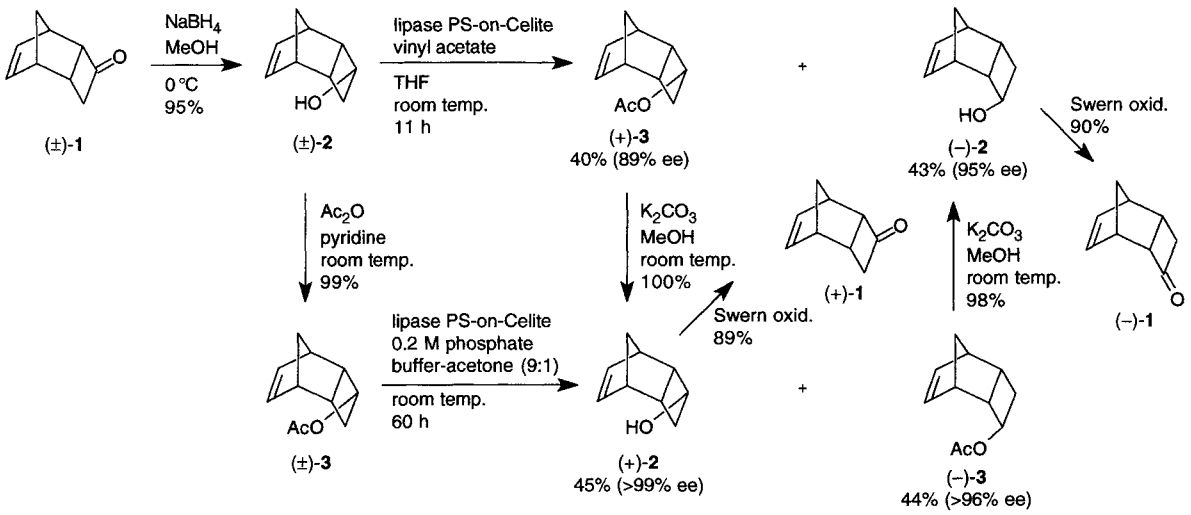
Owing to the high reactivity induced by molecular compression, cyclobutanone derivatives have a considerable synthetic potential for versatile use.[1] We report here the synthesis of an optically active cyclobutanone derivative **1**, sharing its α,β-carbon with 5,6-bonds of bicyclo[2.2.1]heptene, intending to exploit its reactivity and stereochemical background for the stereocontrolled construction of a variety of optically active molecules. Since it is well established that some five-[2] and six[3]-membered ketone homologues of **1** allow highly stereoselective modification around the ketone functionality from the convex face of the molecules and facile thermal retro-Diels-Alder removal of cyclopentadiene leaving the functionalized olefinic products after an appropriate modification, the same situation could readily be assumed for the chiral cyclobutanone **1** rendering it an attractive chiral building block. In order to substantiate this assumption, we examined chiral preparation of **1** by employing lipase-mediated kinetic resolution and determination of the absolute configuration of the chiral **1** obtained by transformation into the structure-defined molecules used for the construction of some natural products.

Racemic tricyclic cyclobutanone[4] {*endo*-tricyclo[4.2.1.$0^{2,5}$]non-7-en-3-one} (±)-**1**, prepared in ~40% overall yield in 4 steps from the Diels-Alder adduct between cyclopentadiene and dimethyl maleate, was reduced with sodium borohydride to give the *endo*-alcohol (±)-**2**, stereoselectively, in 95% yield. We first examined lipase-mediated kinetic transesterification[5] of the resulting racemic alcohol (±)-**2** in an organic solvent containing vinyl acetate. Though clear-cut asymmetric transesterification did not occur, the optically enriched[6] (89% ee) acetate (+)-**3** was obtained in 40% yield leaving the optically enriched[6] (95% ee) alcohol (–)-**2** in 43% recovery when (±)-**2** was stirred with lipase PS (*Pseudomonas* sp., Amano) in tetrahydrofuran (THF) containing vinyl acetate at room temperature for 11 h. Fortunately, the optically enriched alcohol (+)-**2** obtained from the resulting acetate (+)-**3** as well as the recovered (–)-**2** had good crystallinity to give optically pure material,[6] (+)-**2**, mp 59-61 °C; $[\alpha]_D^{28}$ +219.3 (*c* 0.9, $CHCl_3$) and (–)-**2**, mp 59-61 °C; $[\alpha]_D^{28}$ –219.9 (*c* 0.9, $CHCl_3$), in excellent recoveries (>85%) after single recrystallization from a mixture of ether and hexane, respectively.

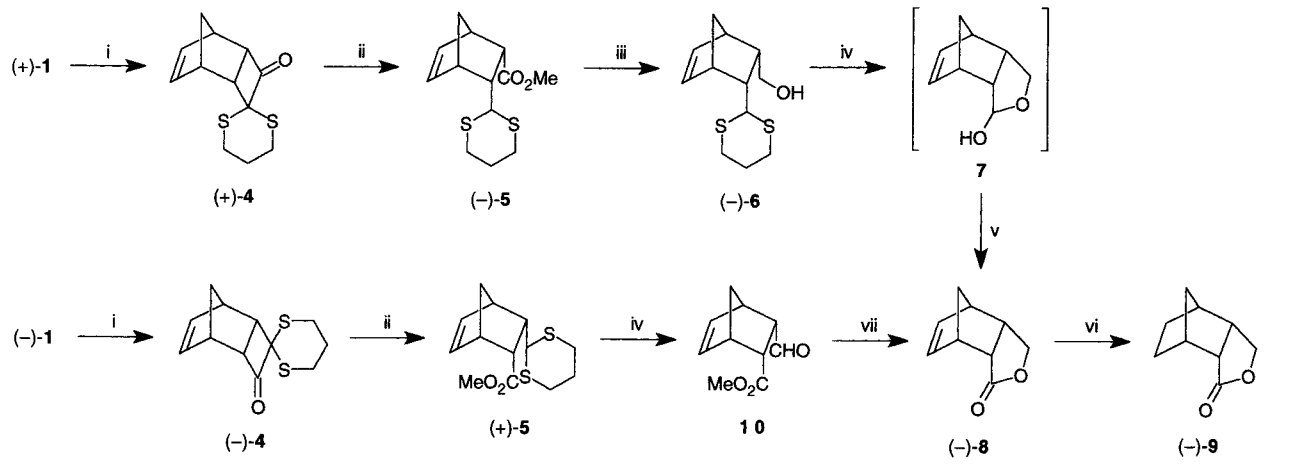
On the other hand, the racemic acetate (±)-**3**, obtained from (±)-**2**, was subjected to hydrolytic conditions[7] using the same lipase in a phosphate buffer solution. The resolution occurred in an enantiocomplementary way to that which occurred in the organic solvent to give the optically pure[6] alcohol (+)-**2** in 45% yield accompanied by the optically enriched[6] (>96% ee) acetate (–)-**3** in 44% recovery after 11 h at room temperature.

Both enantiomers of the optically pure alcohol **2** were transformed into the cyclobutanone **1**, (+)-**1**, $[\alpha]_D^{28}$ +223.8 (*c* 2.0, $CHCl_3$), and (–)-**1**, $[\alpha]_D^{30}$ –222.1 (*c* 2.0, $CHCl_3$), as semisolids having the corresponding stereochemistry in satisfactory yields, respectively, by Swern oxidation[8] (**Scheme 1**).

To determine the absolute configurations of the optically active products thus obtained, we first converted the optically pure (+)-**1** into the α-diketone monothioketal[9] (+)-**4**, mp 114-115 °C; $[\alpha]_D^{30}$ +174.2 (*c* 2.0, $CHCl_3$), in 70% yield on reaction with propane-1,3-dithiotosylate[10] in the presence of potassium *tert*-butoxide. Base-induced cleavage[9,11] of (+)-**4** yielded, excellently, the dithiane-ester (–)-**5**, mp 73-74 °C; $[\alpha]_D^{30}$ –36.5 (*c* 2.0, $CHCl_3$), after esterification, whose ester functionality was reduced to give the primary alcohol (–)-**6**, $[\alpha]_D^{28}$ –80.3 (*c* 2.0, $CHCl_3$). Sequential hydrolysis of the dithiane group[9] and oxidation of the resulting hemiacetal **7** with pyridinium dichromate (PDC) afforded the unsaturated γ-lactone (–)-**8**, mp 119-121 °C; $[\alpha]_D^{28}$ –141.4 (*c* 1.6,

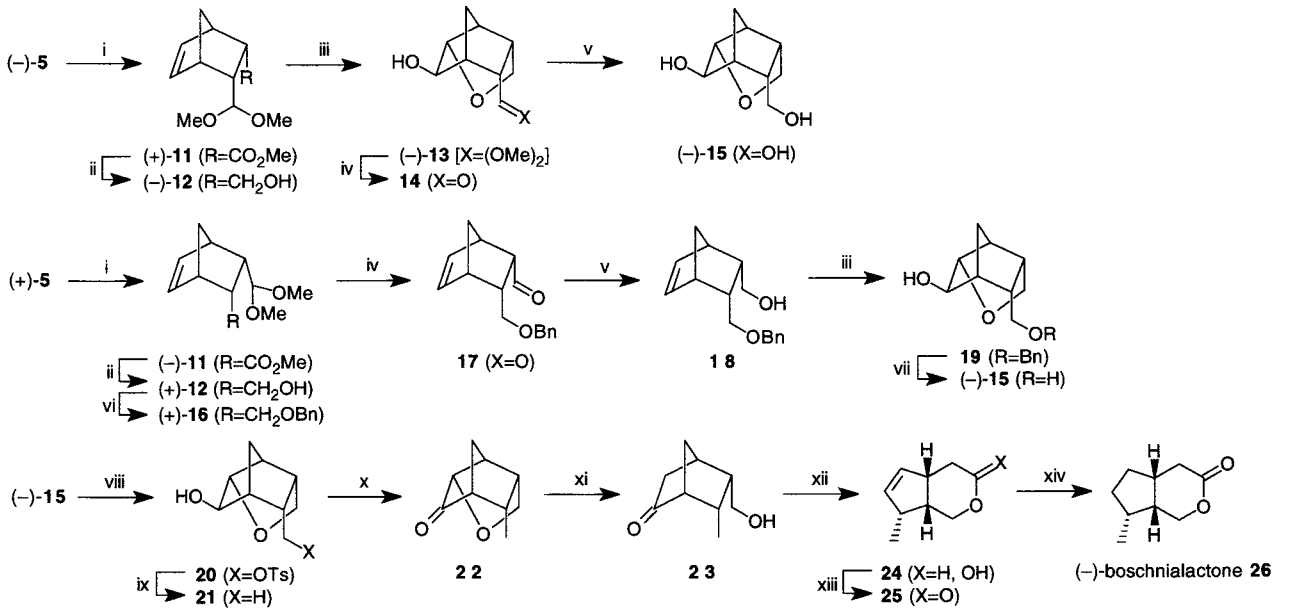


Scheme 1



i) $TsS(CH_2)_3STs$, $KOBu^t$, Bu^tOH-THF (2:7), –20 °C (~70%); ii) KOH, Bu^tOH, 60 °C, acid workup, then CH_2N_2, Et_2O (~98%); iii) $LiAlH_4$, THF, 0 °C (94%); iv), MeI, $NaHCO_3$, MeCN-H_2O (8:1), 40 °C; v) PDC, 4Å sieves, CH_2Cl_2 (71% from **6**); vi) H_2, Pd-C (cat.), AcOEt (~83%); vii) $NaBH_4$, MeOH, room temp. (67% from **5**).

Scheme 2



i) $(CF_3CO_2)_2IPh$, MeOH, 0 °C ~ room temp. (~77%); ii) Bu_2^iAlH, CH_2Cl_2, –78 °C (98%); iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 (~84%); iv) AcOH-H_2O-THF (3:1:1), room temp.; v) $NaBH_4$, MeOH, 0 °C (~61% overall from **12/16**); vi) NaH, BnBr, THF-DMF (4:1); vii) H_2, Pd-C (cat.) (90%); viii) *p*-TsCl (1 mol), Et_3N, DMAP (cat.), CH_2Cl_2, room temp. (74%); ix) $LiAlH_4$, THF, reflux (96%); x) Swern oxid. (83%); xi) Al-Hg, THF-EtOH (1:1), 0 °C (85%); xii) *hv* (254 nm), MeCN, room temp. (41%, 89% based on consumed **23**); xiii) PCC, 4Å sieves, CH_2Cl_2 (90%); xiv) H_2, PtO_2 (cat.), AcOEt (81%).

Scheme 3

$CHCl_3$) [lit.[12]: mp 120-122 °C; $[\alpha]_D^{25}$ +143.2 (*c* 5.2, $CHCl_3$) for the enantiomer], in 71% overall yield. Catalytic hydrogenation of (–)-**8** proceeded without difficulty to give the saturated γ-lactone[13] (–)-**9**, mp 65-66 °C; $[\alpha]_D^{29}$ –145.4 (*c* 1.0, $CHCl_3$) [lit.[13]: $[\alpha]_D^{26}$ +153.28 (*c* 1.01, $CHCl_3$)], in 83% yield. The lactone (–)-**9** was identical in all respects with an authentic (–)-**9** used as the key intermediate[13] for the enantiocontrolled synthesis of the sesquiterpene (+)-β-santalene.

Having established the stereochemistry of the optically active cyclobutanone (+)-**1**, the enantiomeric ketone (–)-**1** was transformed into the enantiomeric (+)-**5**, mp 73-74 °C; $[\alpha]_D^{29}$ +36.8 (*c* 2.2, $CHCl_3$), in a comparable overall yield *via* (–)-**4**, mp 114-115 °C; $[\alpha]_D^{30}$ –174.0 (*c* 2.0, $CHCl_3$), by employing the same procedure above. The dithiane functionality of (+)-**5** was then hydrolyzed to give the aldehyde **10** which, on reduction with sodium borohydride, induced spontaneous cyclization to give the unsaturated lactone (–)-**8**, mp 119-120 °C; $[\alpha]_D^{30}$ –141.9 (*c* 1.0, $CHCl_3$), identical with the product from (+)-**1**, in 67% overall yield. This gave the same saturated lactone (–)-**9**, mp 66-67 °C; $[\alpha]_D^{29}$ –145.8 (*c* 0.8, $CHCl_3$), in 83% yield on hydrogenation. Thus, an enantioconvergent route to β-santalene from both (+)- and (–)-**1** has been established at this point in a formal sense[13] (**Scheme 2**).

To find alternative utility, the dithiane-ester (–)-**5**, prepared from (+)-**1**, was transformed in one step into the acetal (+)-**11**, $[\alpha]_D^{27}$ +52.0 (*c* 1.0, $CHCl_3$), in 77% yield on reaction with *bis*(trifluoroacetoxy)-iodobenzene[14] in methanol. The ester functionality of (+)-**11** was then

reduced with diisobutylaluminum hydride to give the primary alcohol (–)-**12**, $[\alpha]_D^{23}$ –12.4 (*c* 1.0, $CHCl_3$), which, on reaction with *m*-chloroperbenzoic acid,[15] afforded in one step the secondary alcohol (–)-**13**, mp 76-78 °C; $[\alpha]_D^{22}$ –41.4 (*c* 1.0, $CHCl_3$), in 84% yield by spontaneous stereospecific epoxidation and regiospecific intramolecular nucleophilic epoxy-cleavage. The resulting tricyclic alcohol (–)-**13** was transformed into the diol **15**, $[\alpha]_D^{25}$ –24.1 (*c* 1.0, $CHCl_3$), in 61% overall yield *via* the aldehyde **14** by sequential acid hydrolysis and reduction.[15]

The enantiomeric (+)-**5**, on the other hand, was transformed into (+)-**12** in a comparable yield *via* (–)-**11** by employing the same procedure. Benzylation of (+)-**12**, followed by sequential hydrolysis and reduction of the resulting (+)-**16** afforded the primary alcohol **18**, $[\alpha]_D^{26}$ –5.0 (*c* 0.7, $CHCl_3$), in 41% overall yield *via* **17**. On the reaction with *m*-chloroperbenzoic acid, **18** afforded the tricyclic **19**, $[\alpha]_D^{26}$ –38.3 (*c* 0.4, $CHCl_3$), by spontaneous epoxidation and cleavage, whose benzyl ether was removed by hydrogenolysis to give the same diol (–)-**15**, $[\alpha]_D^{23}$ –24.4 (*c* 0.2, $CHCl_3$), in 80% overall yield.

As we have established the enantioconvergent transformation of both enantiomeric **5** into the single enantiomeric product **15**, the resulting diol (–)-**15** was next converted chemoselectively into the secondary alcohol **21**, mp 89-91 °C; $[\alpha]_D^{22}$ –33.9 (*c* 1.5, $CHCl_3$), *via* the monotosylate **20**, $[\alpha]_D^{26}$ –13.3 (*c* 1.0, $CHCl_3$), in 71% overall yield by sequential monotosylation and reductive elimination. The secondary alcohol (–)-**21** obtained was then oxidized to the tricyclic ketone (–)-**22**, mp 66-68 °C; $[\alpha]_D^{21}$ –114.3 (*c* 1.2, $CHCl_3$), in 83% yield, whose ether linkage was cleaved using aluminum amalgam[15] to regenerate the primary hydroxy group to give the hydroxy ketone (+)-**23**, $[\alpha]_D^{21}$ +30.4 (*c* 1.0, $CHCl_3$), in 85% yield. According to the established procedure for the racemate,[15] the optically active ketone (+)-**23** was transformed into the unsaturated δ-lactone[16] (–)-**25**, mp 89-90 °C; $[\alpha]_D^{24}$ –20.2 (*c* 0.4, $CHCl_3$) [lit.[16]: $[\alpha]_D^{25}$ –19.8 (*c* 0.77, $CHCl_3$)], *via* the lactol **24** by sequential photolytic isomerization and oxidation in 36% (80% based on the consumed (+)-**23**) *via* the lactol **24**. Finally, (–)-**25** was hydrogenated in the presence of Adams catalyst to give the target iridoid monoterpene (–)-boschnialactone[16,17] **26**, $[\alpha]_D^{22}$ –18.9 (*c* 0.3, $CHCl_3$) [natural[18]: $[\alpha]_D^{21}$ –18.2 (*c* 2.10, $CHCl_3$); lit.[16]: $[\alpha]_D^{25}$ –21.3 (*c* 0.34, $CHCl_3$)], in 81% yield, which was isolated from the dried terrestrial portion of *Boschniakia rossica* Hult[18] (**Scheme 3**).

Further synthetic studies exploiting the chiral butanone **1** obtained in the present investigation as a chiral building block are in progress.

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(6) Optical purity was determined by a hplc using chiral column (CHIRALCEL OD, elution with 2% *i*-PrOH-hexane) after transformation of the alcohol **2** into its benzoate.

(7) Typical procedure: To a stirred suspension of lipase PS-on-Celite (6.6 g) in 0.2 M phosphate buffer (119 ml) and acetone (13 ml) was added the racemic acetate (±)-**3** (6.6 g, 37.1 mmol) at room temperature and the mixture was stirred for 60 h at the same temperature. The mixture was filtered through a Celite pad and evaporated most of the acetone under reduced pressure. The residue was extracted with ether and the extract was washed (brine), dried ($MgSO_4$), and chromatographed (SiO_2, elution: hexane-Et_2O, 4:1 v/v) to give the alcohol (+)-**2** (2.27 g, 45%, >99% ee[6]) as colorless needles and the acetate (–)-**3** (2.90 g, 44%, >96% ee[6]) as a colorless oil.

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