Organic Process Research & Development **2007**, *11*, 637–641

# A Practical and Scaleable Synthesis of 1*R*,5*S*-Bicyclo[3.1.0]hexan-2-one: The Development of a Catalytic Lithium 2,2,6,6-Tetramethylpiperidide (LTMP) Mediated Intramolecular Cyclopropanation of (*R*)-1,2-Epoxyhex-5-ene

Anthony D. Alorati, Matthew M. Bio, Karel M. J. Brands, Ed Cleator,* Antony J. Davies, Robert D. Wilson, and Chris S. Wise

*Department of Process Research, Merck Sharp & Dohme, Hertford Road, Hoddesdon, EN11 9BU, UK*

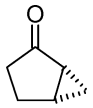
**Abstract:**

**An efficient synthesis of 1*R*,5*S*-bicyclo[3.1.0]hexan-2-one from (*R*)-1,2-epoxyhex-5-ene is described. Development of a catalytic intramolecular cyclopropanation of (*R*)-1,2-epoxyhex-5-ene gives the key homochiral bicycle[3.1.0]hexan-1-ol, which is then oxidized to the desired ketone. This process has been successfully demonstrated on a multi-kilogram scale.**

## Introduction

The cyclopropyl group is a common moiety which appears in a number of natural products and pharmaceutically active compounds.[1] In many cases this function appears in the form of a fused bicycle, and there is often the requirement for such bicycles to be enantiopure. A short and scalable method to generate these intermediates, in an enantiopure fashion and containing functionality for further elaboration, would therefore be desirable. Whilst there are a number of methods for generating 1,1′,5-trisubstituted bicyclic-2-ketones,[2] there are far fewer examples for obtaining the enantiopure 1,5-disubstituted fused systems.[3] During the course of an ongoing project we required multi-kilogram quantities of 1*R*,5*S*-bicyclo[3.1.0]hexan-1-one **1** (Figure 1). This compound is not available from commercial sources in either racemic or enantiopure form.

Previous syntheses of **1** have generally been performed in a racemic fashion. One of the most direct transformations involves the reaction of trimethylsulfoxonium ylide with cyclopent-2-en-1-one.[4] Whilst this reaction was found to afford an excellent 92% yield when performed in the racemic sense, a chiral variant of this reaction is unknown. Another common method of cyclopropanation is the Simmons−Smith reaction. It has been shown that the alcohol function in cyclopent-2-en-1-ol is able to direct this reaction such that *syn*-products are formed exclusively.[5] Unfortunately, the lack of an efficient route to the chiral starting material rendered a Simmons−Smith/oxidation route to **1** unpractical. Mash et al. have used a chiral auxiliary based Simmons−Smith approach to generate **1** from cyclopent-2-en-1-one.[6,7] This approach, however, requires extended reaction times for formation of the acetal substrate and affords modest yields for the key cyclopropanation event, even though the diastereoselectivty is generally quite good (dr up to 13:1). There has also been considerable effort in the synthetic community evaluating metal-catalyzed cyclopropanations of suitably functionalized α-diazoketones. Rhodium[8] and copper[9] based chiral catalysts have been employed, with the rhodium systems giving marginally higher enantioselectivities (87 vs 77% ee, respectively) and much better yields (96 vs 54%, respectively). However, these methods are not economically viable on a larger scale due to the high costs for the catalysts, and these were thus not considered.



**1**

***Figure 1.*** **1*R*,5*S*-Bicyclo[3.1.0]hexan-2-one 1.**

## Results and Discussion

Work by Hodgson et al.[10] has outlined an expedient and highly diastereoselective synthesis of *trans*-bicyclo[3.1.0]hexan-2-ols, including the synthesis of 1*R*,2*R*,5*S*-bicyclo[3.1.0]hexan-2-ol **4**, starting from enantiopure epoxy alkenes such as **2**. The proposed mechanism is that deprotonation of **2** with a strong hindered base such as LTMP results in α-lithiation of the epoxide. This deprotonation has been shown to occur exclusively *trans* to the *β*-alkyl chain. Subsequent intramolecular cyclization of the carbenoid intermediate occurs *via* the chair transition state **3** to provide **4** (Scheme 1). This reaction was found to proceed with excellent retention of enantiopurity.

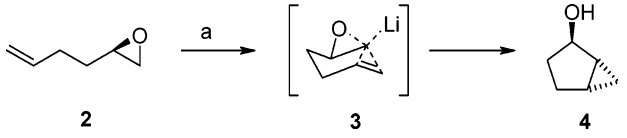
The Hodgson group also reported on a further refinement to the synthesis of *trans*-bicyclo[3.1.0]hexan-2-ols by generating the precursor epoxides *in situ* from chlorohydrin **6** (Scheme 2).[11] The latter could be prepared by copper catalysed ring opening of epichlorohydrin **5** with a suitable

* To whom correspondence should be addressed. E-mail: edward_cleator@merck.com.

(1) Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 977.
(2) (a) Johansson, C. C. C.; Bremeyer, N.; Ley, S. V.; Owen, D. R.; Smith, S. C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6024. (b) Bremeyer, N.; Ley. S. V.; Smith, S. C.; Gaunt, M. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 2681.
(3) Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1.
(4) Newman-Evans, R. H.; Simon, R. J.; Carpenter, B. K. *J. Org. Chem*. **1990**, *55*, 695.
(5) Friedrich, E. C.; Briesaw, G. *J. Org. Chem*. **1982**, *47*, 1615.
(6) Mash, E. A.; Hempley, S. B.; Nelson, K. A.; Heidt, P. C.; Van Deusen, S. *J. Org. Chem*. **1990**, *55*, 2045.
(7) Mash, E. A.; Hempley, S. B. *J. Org. Chem*. **1990**, *55*, 2055.
(8) Barberis, M.; Pérez-Prieto, J.; Salah-Eddine, S.; Lahuerta, P. *Org. Lett.* **2001**, *3*, 3317.
(9) Dauben, W. G.; Hendricks, R. T.; Luzzio, M. J.; Ng, H. P. *Tetrahedron Lett.* **1990**, *31*, 6969.
(10) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *J. Am. Chem. Soc*. **2004**, *126*, 8664.

10.1021/op700042w CCC: $37.00 
Published on Web 04/18/2007

***Scheme 1***[a]

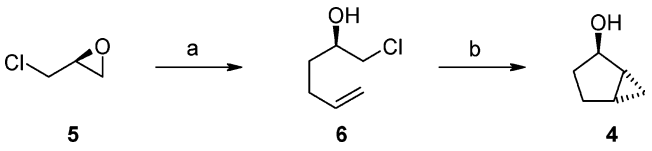



**2** **3** **4**

[a] Reagents and conditions: (a) 0.2 M LTMP in MTBE added to a 0.2 M solution of **2** over 1 h at 0 °C and then warmed to rt over 16 h.

Grignard reagent such as allylmagnesium chloride. A one-pot ring closure and intramolecular cyclopropanation of **6** then proceeds to give **4**. Whilst this protocol allows for the synthesis of compounds such as **4**, the yields for this two-step sequence are lower than those for the direct cyclopropanation described in Scheme 1. Moreover, a total of 3.5 equiv of *n*-BuLi and 2.5 equiv of TMP are required.

***Scheme 2***[a]

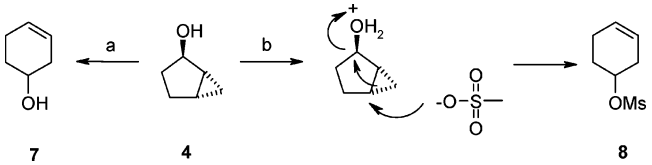



**5** **6** **4**

[a] Reagents and conditions: (a) allylmagnesium chloride, CuI (0.1 equiv), THF, −78 °C → 20 °C, 75%; (b) *n*-BuLi (3.5 equiv), TMP (2.5 equiv), MTBE, 0 °C for 2 h then 20 °C for 16 h, 65%.

As (*R*)-1,2-epoxyhex-5-ene **2** is commercially available, we decided to investigate the Hodgson methodology as a potential route to **1**. Initially, we repeated the original conditions: namely, addition of a freshly prepared 0.2 M solution of LTMP in methyl *tert*-butyl ether (MTBE) to a 0.2 M solution of **2** in MTBE at 0 °C. After warming to ambient temperature and aging for an additional 16 h, the reaction was quenched and worked up as described. $^1$H NMR analysis of the crude reaction mixture after workup indicated an approximate 90% recovery. We were therefore surprised that in our hands purification by column chromatography, as described, led only to a modest isolated yield of 38%. The balance of the material was found to be the ring opened alcohol **7**. The acid sensitivity of **4** was confirmed by treatment of a $CDCl_3$ solution of **4** with methanesulfonic acid (MSA). After aging overnight, a clean conversion to mesylate **8** was observed (Scheme 3). To overcome this acid instability initial lab scale samples were therefore purified by distillation.

***Scheme 3***[a]




**7** **4** **8**

[a] Reagents and conditions: (a) $SiO_2$, chromatography, 52% of **7**, 38% of **4**; (b) $CDCl_3$, MsOH, rt quantitative.

The acid sensitivity of **4** during the workup caused some concern, and the stability of a solution of **4** after 20 h was examined for a series of acids and buffers (Table 1).

The stress test clearly showed that quenching of the reaction mixture with strong acids should be avoided, even though the instability of **4** can be modulated by lowering the concentration of the acid (entry 3). Quenching the reaction mixture with acetic acid led to the precipitation of the TMP acetate. Dissolution of this solid required impractically large volumes of water, and due to the significant water solubility of **4**, numerous back extractions with MTBE were required to recover the product with an acceptable yield. An alternative procedure was to quench the reaction mixture with a stoichiometric charge of acid to keep the effective concentration of acid low and minimize the amount of water. Thus, quenching the reaction mixture at 0 °C with 1 equiv of 3 M HCl (with respect to the total amount of basic species present) followed by a second wash with 1 equiv of 3 M HCl (with respect to the amount of TMP charged) generated an MTBE stream which was free of TMP and which was sufficiently pure to be used without any further purification in the next step. The product yield could be maximized via a single back extraction with MTBE. This version of the Hodgson's procedure containing an optimized workup was found to reproducibly afford **4** in 86% assay yield.

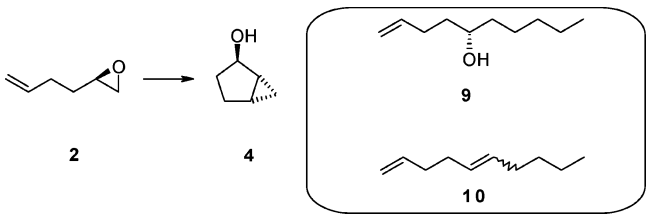
***Table 1.*** **Stress test of 4 with acids/buffers**

| entry[a] | acid/buffer | ratio[b] **7:4** |
|---|---|---|
| 1 | 6 M HCl | 100:0 |
| 2 | 3 M HCl | 100:0 |
| 3 | 1 M HCl | 60:40 |
| 4 | pH 4 buffer | 5:95 |
| 5 | acetic acid | 0:100 |
| 6 | citric acid | 0:100 |
| 7 | pH 7 buffer | 0:100 |

[a] 1 mL of a 0.1 M MTBE solution of **4** aged overnight at room temperature in the presence of 1 mL of the appropriate acid/buffer. [b]Ratio determined by $^1$H NMR.

Our attention then turned to the optimization of the cyclization reaction itself. The procedure described by Hodgson et al. is performed at high dilutions, partly due to the low solubility of LTMP in MTBE (this solvent is critical for the success of this transformation), making this procedure unworkable on a larger scale. We envisaged that this problem could be solved by changing the order of addition of the reactants. Towards this end, the stability of **2** in the presence of 2.5 M *n*-BuLi at 0 °C was assessed. According to GC analysis compounds **4**, **9**, and **10** were formed in an area ratio of 3:67:40, respectively (Scheme 4).

***Scheme 4.*** **Optimization of the cyclization 2 → 4**

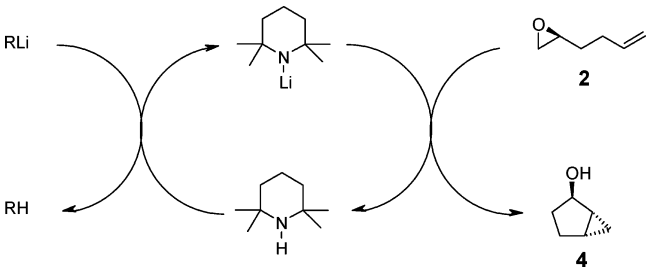



**2** **4** **9** **10**

However, addition of a concentrated solution of **2** (7 mL/g) to a 0.2 M solution of preformed LTMP in MTBE at 0 °C yielded **4** in practically the same assay yield as that described above (84%). The same result was also obtained when a 0.2 M solution of **2** in MTBE containing 2 equiv of TMP was treated with 2.5 M *n*-BuLi at 0 °C. Moreover, the

(11) Hodgson, D. M.; Chung, Y. K.; Paris, J.-M. *Synthesis* **2005**, 2264.

***Table 2.*** **Catalytic intramolecular cyclopropanations**




| entry[a] | TMP (equiv) | RLi (equiv) | solvent | yield[b] |
|---|---|---|---|---|
| 1 | 1 | *n*-BuLi (2) | MTBE | 95% |
| 2 | 0.5 | *n*-BuLi (2) | MTBE | 97% |
| 3 | 0.5 | *n*-BuLi (1.1) | MTBE | 95% |
| 4 | 0.25 | *n*-BuLi (1.1) | MTBE | 85% |
| 5 | 0.05 | *n*-BuLi (1.1) | MTBE | 63% |
| 6[c] | 0.25 | *n*-BuLi (1.1) | MTBE | 91% |
| 7 | 0.5 | *n*-HexylLi (1.1) | Hexanes | 80% |
| 8 | 0.5 | *n*-HexylLi (1.1) | MTBE | 90% |

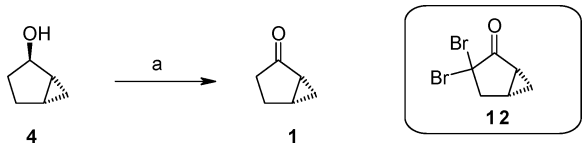
[a] RLi added to a stirred solution of **2** and TMP in 10 volumes of solvent (with respect to **2**) over 4 h maintaining an internal $T \leq 0$ °C, unless otherwise stated. [b]Quoted yields are GC assay yields determined with biphenyl as an internal standard. [c]5 volumes of solvent with respect to **2**.

concentration of the reaction could also be increased with no impact on the yield. Thus, when **2** and 2 equiv of TMP in 10 volumes of MTBE at 0 °C were treated with 2 equiv of 2.5 M *n*-BuLi over 1 h, the assay yield was 86%. Most importantly, it proved possible to reduce the amount of TMP to substoichiometric (i.e., catalytic) amounts (Table 2). The rate of *n*-BuLi addition proved to be the key in making this concept feasible. Whilst quick additions of *n*-BuLi led to poor reaction profiles and relatively low assay yields, a slow addition rate provided excellent profiles with improved assay yields (Table 2, entry 1). The best results were achieved when *n*-BuLi was added over 4 h. It was demonstrated that both free *n*-BuLi and prolonged exposure of **2** to the lithium alkoxide of **4** results in formation of undesired byproducts.

Entry 2 shows that reducing the amount of TMP from 1.0 to 0.5 equiv does not effect the assay yield. Moreover, it proved possible to perform this reaction with a near theoretical amount of *n*-BuLi without a loss in yield (entry 3). When the amount of TMP is further reduced to 0.25 equiv, the yield becomes lower at the same concentration (entry 4). However, when the concentration is increased, the yield returns are >90% (entry 6). A slight drop in the efficiency of the reaction was observed on lowering the amount of TMP to 0.05 equiv (entry 5). This is believed to be a consequence of a slow turnover of LTMP. The presence of significant amounts of free *n*-BuLi under these conditions presumably leads to the side reactions. These reactions can also be carried out with *n*-HexylLi rather than *n*-BuLi (entry 8), the latter also allowing a change to hexane as the solvent (entry 7). The conditions in entry 3 (0.5 equiv of TMP and 1.1 equiv of *n*-BuLi) were deemed optimal and reproducibly yielded **4** in 92−97% assay yield on a 1−200 g scale.[12]

With a robust method for the production of **4** in hand, attention turned to the oxidation of **4** to furnish the desired ketone **1**. On a small scale this was accomplished quite conveniently by using a TPAP/NMO oxidation.[13] However, these conditions are significantly exothermic, and a safer alternative was sought. After evaluating a number of alternatives we eventually settled on a TEMPO/bleach oxidation.[14] This reaction was performed in a two-phase system consisting of MTBE and buffered aqueous bleach with a catalytic amount of TEMPO (2.5 mol %) and potassium bromide (15 mol %). The success of the reaction proved critically dependent on the pH. At lower pH's (5−8) the oxidation was incomplete, whilst at high pH (>11) the dibrominated **12** was formed as a significant byproduct (Scheme 5). The

***Scheme 5.*** **Oxidation of alcohol 4[a]**




[a] Reagents and conditions: TEMPO (2.5 mol %), NaOCl (11.7 w/w % available chlorine, 1.6 equiv), MTBE, $H_2O$, $K_2PO_4$ (1.5 equiv), $KhPO_4$ (to adjust pH to ~8.8 − 8.9), KBr (15 mol %), 95%.

optimal pH window was found to be 8.5−10.5. Thus, utilizing 1.5 mol equiv of dibasic potassium phosphate (~ pH 9.5), and adjusting the pH to 8.80−8.90 by the addition of monobasic potassium phosphate, led to a buffer which maintained the pH in the optimal range 10.0−10.5 during the bleach addition. Even though the reaction works equally well with conventional dilute bleach (typical 4.7% w/w available chlorine assay), we preferred to perform the reaction with commercially available concentrated bleach solution (typically 11.7% w/w available chlorine assay) in order to keep the total volume of the aqueous reaction solution to a minimum. The more dilute conditions required numerous MTBE extractions of the aqueous layer to recover the product with an acceptable yield. Using the more concentrated conditions, only two back extractions of the aqueous layer with MTBE were typically required to achieve complete product recovery (92−95% overall yield).

On a lab scale a distillation provided the desired **1** with >95% recovery from the crude oxidation stream. The distilled ketone was typically 90−95 wt % pure and was found to perform well in our subsequent chemistry.

The above-described intramolecualar cyclopropanation and oxidation reactions were successfully demonstrated on the 7.5 kg scale and provided **1** with ee > 99.5%. It should be noted that the lower cooling capacity of our chosen vessel required a much longer *n*-BuLi addition time. Nevertheless, the cyclization yield was still found to be 86% under these conditions. After the workup and a concentration of the product stream to approximately 5 mL/g, we obtained an MTBE stream containing 82% of **4** by assay (3 and 1% of **4** were lost to the distillate and aquous layer, respectively). Oxidation of this stream under the reported conditions yielded **1** in 96% isolated (2% were lost to the aqueous layer).

In summary, a highly practical, efficient, and robust procedure for the intramolecular cyclopropanation of (*R*)-1,2-

(12) Bio, M. M.; Brands, K. M. J.; Cleator, E. Patent WO2007/015111 A1.
(13) Langer. P. *J. Prakt. Chem.* **2000**, *347*, 728.
(14) Anelli, P. L.; Biffi, C.; Montanari, F.; Quici, S. *J. Org. Chem.* **1987**, *52*, 2559.

epoxyhex-5-ene (**2**) followed by oxidation of the resulting (1*R*,2*R*,5*S*)-bicyclo[3.1.0]hexan-2-ol (**4**) to the desired (1*R*,5*S*)-bicyclo[3.1.0]hexan-2-one (**1**) was developed. Most notably, the first step of this sequence uses a catalytic amount of base rather than the superstoichiometric amount reported in the literature.

## Experimental Section

**GC Conditions for the Determination of Enantiomeric Purity of Epoxide 2**:

Column: RT-GammaDEXsa, 30 m, 0.32 mm id, 0.25 $\mu$m df

Flow: Helium at 10 psi

Injector temperature: 200 °C

Detector temperature: 200 °C

Oven temperature: 40 °C

Run time: 60 min

Sample dissolved in methanol (e.g., 50 $\mu$L in 5 mL)

Split flow: 50:1

Injection volume: 1 $\mu$L

Retention times for desired and minor enantiomers 46.5 and 50.7 min, respectively.

**(1*R*,2*R*,5*S*)-Bicyclo[3.1.0]hexan-2-ol 4.** (*R*)-1,2-Epoxyhex-5-ene (7.5 kg, 1 equiv) was charged to the vessel containing MTBE (75 L, 10 volumes). To this solution was added tetramethylpiperidine (5.4 kg, 0.5 equiv), and the reaction mixture was cooled to between −5 and 0 °C. *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added at such a rate so as to maintain the temperature between −5 and 0 °C (12 h total addition time). The resulting pale orange reaction mixture was maintained at <0 °C overnight, after which all starting epoxide had been consumed (assay for 86% yield by GC). The reaction was then quenched by the addition of 3 N HCl (40.8 L, 122.3 mol, 1.6 equiv). The aqueous phase was cut and retained. The organic phase was washed again with 3 M HCl (12.7 L, 38.2 mol, 0.5 equiv). The combined aqueous cuts were then back extracted twice, first with 38 L of MTBE (5 volumes) and finally with 19 L (2.5 volumes). The organic phases were combined and concentrated by vacuum distillation at a <30 °C pot temperature to give the alcohol as a solution in approximately 38 L of total volume. This pale yellow oil was assayed for 6.2 kg of (1*R*,2*R*,5*S*)-bicyclo-[3.1.0]hexan-2-ol **4** (82% yield) and was used directly in the oxidation step. N.B. there was found to be 3% in the distillate and 1% in the aqueous cut by assay.

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ −0.07−0.00 (m, 1H), 0.38−0.47 (m, 1H), 1.27−1.37 (m, 2H), 1.38−1.43 (m, 1H), 1.53 (dd, $J$ = 8.4, 14.4 Hz, 1H), 1.65 (dd, $J$ = 8.0, 12.4 Hz, 1H), 1.83 (s, 1H, OH), 1.87−1.98 (m, 1H), 4.21 (d, $J$ = 4.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 6.9, 16.1, 24.2, 24.5, 30.3, 74.3.

GC Conditions

Column: HP 5 (30 m × 0.53 $\mu$m × 1.5 $\mu$m)

Oven conditions

Initial temperature: 60 °C

Initial time at 60 °C: 3.0 min

12.0 °C/min ramp to final temperature of 200 °C.

Final time at 200 °C: 4.0 min

Inlet temperature (split mode with a ratio of 4.759:1): 220 °C

**Retention times**

| | |
|---|---|
| 2-(but-3-enyl)oxirane **2** | 4.9 min |
| bicyclo[3.1.0]hexan-2-ol **4** | 6.7 min |
| Diene **10** | 8.2 min |
| Alcohol **9** | 10.4 min |

**(1*R*,5*S*)-Bicyclo[3.1.0]hexan-2-one 1.** To the MTBE solution of bicyclo[3.1.0]hexan-2-ol from step 1, 30.5 kg of water were added followed by dibasic potassium phosphate (16.24 kg, 93.2 mol, 1.48 equiv). The batch was then held over the weekend. The mixture was cooled to 0 °C, and then TEMPO was charged (0.243 kg, 1.56 mol, 2.5 mol %). Sodium hypochlorite (67.7 mol) was added slowly to the vigorously stirred mixture over 6 h maintaining the internal temperature at <5 °C. GC analysis showed approximately 20% of starting material remained and the pH was at 10.4. An additional 14.1 mol of bleach were added to give 13.7% of remaining starting material. At this point an additional charge of TEMPO (0.1 kg) and monobasic potassium phosphate (0.96 kg) was made, and then an additional 18.8 mol of bleach were added. GC then showed complete conversion of all starting material. A total of 1.63 mol of bleach were required to reach full conversion of the alcohol. The oxidation reaction was then quenched by addition of $Na_2SO_3$ aqueous solution until the reaction was negative for oxidant by starch iodide indicator paper (2.78 kg, 35 mol %). The quenched reaction was allowed to sit at room temperature overnight. The aqueous phase was then cut and drummed. The organic phase was also drummed out of the vessel. The aqueous phase was extracted twice with 28 kg of MTBE and 14 kg of MTBE, respectively. All organic cuts were combined and assayed for 5.75 kg, 95% yield.

$^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 0.90 (m, 1H), 1.16 (m, 1H), 1.73 (m, 1H), 2.05 (m, 5H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 13.5, 21.6, 22.6, 27.4, 31.4, 215.1.

GC Conditions as those above.

**Retention times**

| | |
|---|---|
| bicyclo[3.1.0]hexan-2-ol **4** | 6.70 min |
| bicyclo[3.1.0]hexan-2-one **1** | 7.71 min |

HPLC Conditions

Column: Phenomenex Luna C18, 3 $\mu$ (150 mm × 4.6 mm)

Column temperature: 35 °C

Flow rate: 1.0 mL/min

Wavelength: 210 nm

A = 0.1% aqueous phosphoric acid solution

B = acetonitrile

**HPLC Conditions**

| Time | A% | B% |
|---|---|---|
| 0 | 90 | 10 |
| 20 | 10 | 90 |
| 25 | 10 | 90 |
| 27 | 90 | 10 |
| 35 | 90 | 10 |

**Retention Times**

| | |
|---|---|
| bicyclo[3.1.0]hexan-2-one | 6.22 min |

**GC Conditions for the Determination of Enantiomeric Purity of Ketone 1:**

Column: RT-GammaDEXsa, 30 m, 0.32 mm id, 0.25 $\mu$m df

Flow: Helium at 10 psi

Injector temperature: 200 °C

Detector temperature: 200 °C

Oven temperature: 110 °C

Run time: 30 min

Sample dissolved in methanol

Retention times of desired and minor enantiomers 22.0 and 24.3 min, respectively.


## Acknowledgment

We thank Sophie Strickfuss and Andy Kirtley for their help with GC−MS and Chiral HPLC analyses.

Received for review February 16, 2007.

OP700042W