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Chiral modification of adamantane

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Abstract—Three optically active adamantane derivatives have been constructed starting from *meso* 7-methylidenebicyclo[3.3.1]nonan-3-one by employing two chirality induction processes, asymmetric aldolization and Sharpless asymmetric epoxidation. © 2002 Published by Elsevier Science Ltd.

Considerable interest has been shown recently in adamantane derivatives for medicinal use.[1] Although chirality is one of the most important factors for their physiological activities, only one example of the introduction of chirality introduced in the adamantane nucleus has been reported to date by Hirose and coworkers,[2] employing enzymatic reduction. We are, therefore, interested in developing a convenient method which allows chiral modification of adamantane derivatives for future use. We report here two simple methods for the preparation of optically active adamantane derivatives by employing an asymmetric aldol reaction[3] and the kinetic resolution under Sharpless asymmetric epoxidation conditions,[4] respectively, starting from the common *meso* symmetric 7-methylidene[3.3.1]nonan-3-one **1**.[5]

Thus, the ketone **1** was treated with the amide generated in situ from (*R*,*R*)-*N*,*N*-di-2-phenylethylamine[3,6] and butyllithium in THF at −78°C in the presence of 2 equiv. of lithium chloride, followed by benzaldehyde at the same temperature. Two isomeric products were obtained as readily separable crystals in yields of 71 and 8%. The major isomer was determined as (α-*S*, β-*R*)-β-ketol **4**, on the basis of the empirical rule[3] and the inherent stereochemical nature of the bicyclic ketone **1**. Namely, the reaction occurred diastereoselectively from the convex face onto the pro-*R* center of the enolate **2**, enantioselectively generated by the chiral amide to give the major product through the β-ketoalkoxide **3** although the stereochemistry of the minor isomer could not be determined. The optical purity of the major product **4** was determined as 74% ee by HPLC (CHIRALCEL OD, elution with Pr^{i}OH–hexane, 3:97) after transformation into the benzylidene derivative **7**. However, it could be enantiomerically purified by recrystallization from pet. ether in 56% recovery to give the optically pure ketol **4**, mp 102–103°C, $[\alpha]_D^{26}$ +16.9 (*c* 1.3, $CHCl_3$). On mesylation followed by immediate treatment of the resulting mesylate **5** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the ketol **4** afforded the single benzylidene ketone **7**, mp 102°C, $[\alpha]_D^{26}$ +618.2 (*c* 0.8, $CHCl_3$), as colorless prisms (>99% ee by HPLC: CHIRALCEL OD, elution with Pr^{i}OH–hexane, 3:97). The stereochemistry of the olefin moiety was determined as *E* due to a significant NOE between the aromatic (*o*-H: δ 7.17) and the angular hydrogen (δ 3.34) in its ^{1}H NMR spectrum (C_6D_6). This also indicated that the stereochemistry of the hydroxy functionality of the β-ketol is that shown in **4** since the *E*-olefin **7** may be expected to arise only through the enolate intermediate represented by **6** though unambiguous determination of the structure of the β-ketol **4** still to be required.

Acid-catalyzed cyclization of the benzylidene ketone **7** was first examined to give the adamantane framework because the acid-catalyzed formation of adamantane derivative from the *meso* precursor **1** has been reported.[7] As expected, when the enantiopure enone **7** is exposed to 35 mol% of Ti(IV) chloride in CH_2Cl_2 at −30°C, a facile cyclization occurs to give the benzylidene adamantane (+)-**8**, mp 124–126°C, $[\alpha]_D^{26}$ +49.2 (*c* 0.4, $CHCl_3$), as a single product in 86% yield. The stereochemistry of the olefin moiety of the adamantane (+)-**8** was determined as *E* by observation of an NOE between the aromatic proton (*o*-H: δ 7.15) and the angular proton (δ 3.40) in its ^{1}H NMR spectrum ($CDCl_3$).

When the enantiopure enone **7** was first treated with the cuprate reagent, generated in situ from methyllithium

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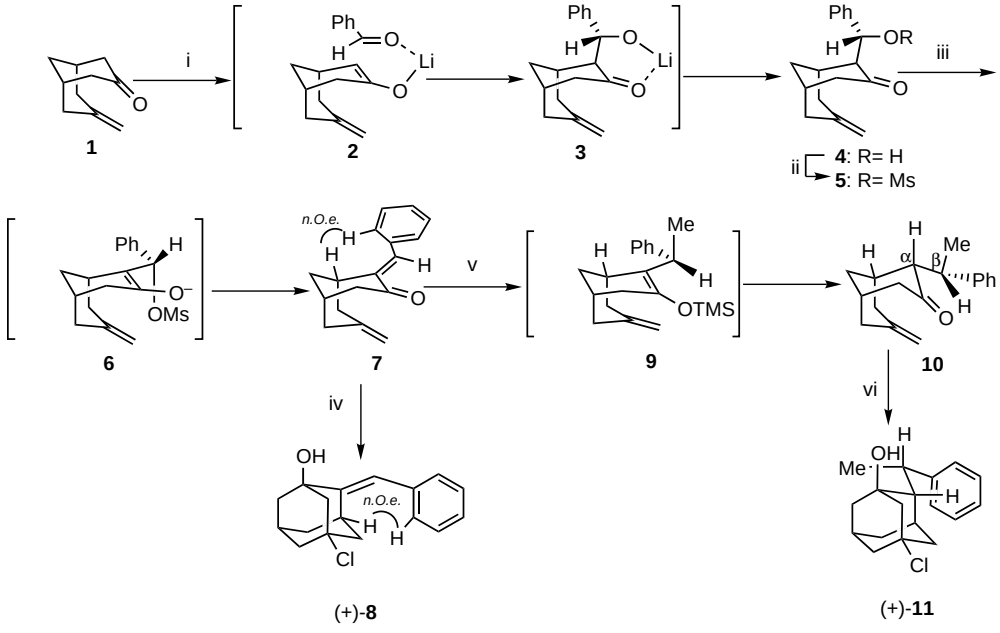
and Cu(I) Br-dimethyl sulfide complex in THF, in the presence of TMS–Cl and HMPA,[8] the 1,4-addition product **10**, mp 86–87°C, $[\alpha]_D^{26}$ +164.2 (*c* 0.3, $CHCl_3$), was obtained as a single product after workup with diluted hydrochloric acid. Since both the 1,4-addition to the enone **7** and the protonation of the silyl enol ether intermediate **9** should occur from the convex-face, the stereochemistry of the α-(1-phenylethyl)ketone **10** was presumed to be the (α-*R*, β-*S*) configuration.

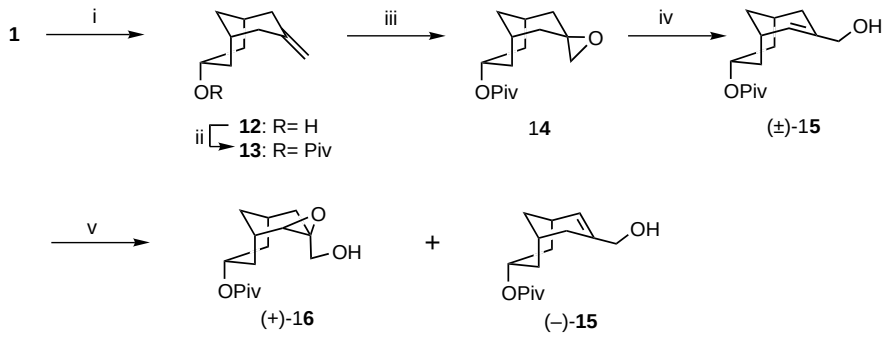
On exposure to 5 mol% of Ti(IV) chloride in CH_2Cl_2 at −30°C, the ketone **10** furnished the saturated adamantane (+)-**11**, $[\alpha]_D^{25}$ +72.0 (*c* 0.9, $CHCl_3$), as a colorless oil in quantitative yield by facile cyclization while retaining the stereochemistry of the precursor **10** (Scheme 1).

The second example utilized kinetic resolution during the Sharpless asymmetric epoxidation.[4] The same *meso*-ketone **1** was first transformed into the pivalate **13** by reduction with diisobutylaluminum hydride (DIBAL) in dichloromethane, followed by treatment of the resulting *endo*-alcohol **12**, mp 50–55°C, with pivaloyl chloride under basic conditions. Reaction of the pivalate **13** with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of $NaHCO_3$ took place diastereoselectively to give the epoxide **14**, mp 96–98°C, as a single product. It was found that the rearrangement of the epoxide **14** occurred in a surprisingly facile manner when it was stirred in chloroform at 30°C for 2 h to furnish the allyl alcohol (±)-**15** in 84% yield. Kinetic resolution was carried out under catalytic conditions[4,9] in the presence of 15 mol% of diisopropyl L-tartrate (DIPT), 10 mol% of Ti(IV) isopropoxide and 65 mol% of *tert*-butyl hydroperoxide (TBHP) in dichloromethane suspended with molecular sieves (3 Å) at −20°C to give the optically enriched epoxide (+)-**16**, mp 92–93°C, $[\alpha]_D^{28}$ +28.2 (*c* 0.4, $CHCl_3$), in 62% yield leaving the optically enriched allyl alcohol (−)-**15**, $[\alpha]_D^{26}$ −101.1 (*c* 0.4, $CHCl_3$) in 38% yield. The optical purity of the products was determined as 53 and 96% ee by HPLC (CHIRALCEL OD, elution with Pr^iOH–hexane, 1:99 for **16** and 1:9 for **15**) after conversion into the corresponding *p*-nitrobenzoates (Scheme 2).

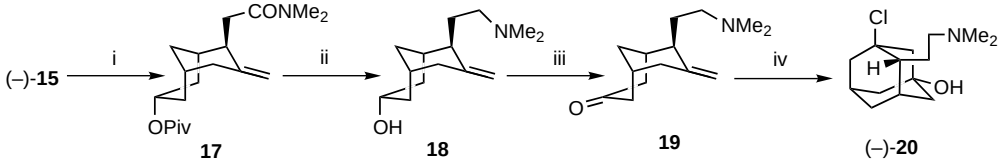
In order to transform the optically enriched allyl alcohol (−)-**15** (96% ee) thus obtained into the adamantane derivative, it was refluxed with dimethylacetamide dimethyl acetal in diphenyl ether at 280°C to give the tertiary amide **17**, mp 80–81°C, $[\alpha]_D^{28}$ −15.9 (*c* 0.8, $CHCl_3$), stereoselectively, as a single product in 94% yield. The reaction was presumed to occur exclusively from the convex-face to give the product **17** having the β-acetamide configuration which was supported by the ^1H NMR spectrum. Namely, the coupling constants between the vicinal allylic methine proton appeared at δ 2.69 and angular methine proton was very small (<1 Hz), indicating their dihedral angle to be near 90° which is expected for **17** upon examination of models. Reduction of the amide **17** with lithium aluminum hydride proceeded with concomitant removal of the pivaloyl functionality to give the amino-alcohol **18**, $[\alpha]_D^{28}$ −15.9 (*c* 0.8, $CHCl_3$), as a colorless oil. Oxidation of the amino-alcohol **18** with a catalytic amount of tetrapropylammonium perruthenate (TPAP)[10] in the presence of *N*-methylmorpholine *N*-oxide (NMO) proceeded without difficulty to give the amino-ketone **19**, $[\alpha]_D^{28}$ −15.9 (*c* 0.8, $CHCl_3$), quantitatively. Finally, the amino-ketone **19** was exposed to Ti(IV) chloride[7] as above to furnish the enantiomerically enriched adamantane (−)-**20**, $[\alpha]_D^{29}$ −36.7 (*c* 0.4, $CHCl_3$), in 62% yield (Scheme 3).



Scheme 1. *Reagents and conditions*: (i) (*R*,*R*)-$(PhCHMe)_2NH$, LiCl (2 equiv.), BuLi, THF, −78°C, PhCHO. (ii) Ms–Cl, Et_3N, CH_2Cl_2. (iii) DBU, toluene (93%, two steps). (iv) $TiCl_4$, CH_2Cl_2, −30°C (86%). (v) MeLi, CuBr–Me_2S, TMS–Cl, HMPA, THF, −78°C then 10% HCl (91%). (vi) $TiCl_4$, CH_2Cl_2, −30°C (100%).



Scheme 2. *Reagents and conditions*: (i) DIBAL, CH_2Cl_2, −78°C (91%). (ii) Piv–Cl, Et_3N, DMAP (cat.), CH_2Cl_2. (iii) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 (67%, two steps). (iv) $CHCl_3$, 30°C, 2 h (84%). (v) (*R*,*R*)-DIPT, $Ti(OPr^i)_4$, TBHP, molecular sieves (3 Å), CH_2Cl_2, −20°C, 20 min.



Scheme 3. *Reagents and conditions*: (i) $MeC(OMe)_2NMe_2$, Ph_2O, 280°C (94%). (ii) $LiAlH_4$, THF (87%). (iii) TPAP, NMO, molecular sieves (4 Å), $MeCN–CH_2Cl_2$ (100%). (iv) $TiCl_4$, CH_2Cl_2, 30 ~ 0°C, 2 h (62%).

In conclusion, we have developed two convenient methods for the preparation of enantiomerically pure and highly enantiomerically enriched adamantane derivatives starting from a common *meso* symmetric precursor. Since the methods developed are highly flexible, they may be used for the construction of a variety of chiral adamantane derivatives.

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