Sequential "Double-Michael" Additions of Dienolates with C_{60}: Rapid Access to Sterically Congested Buckminsterfullerene Derivatives with Defined Stereochemistry

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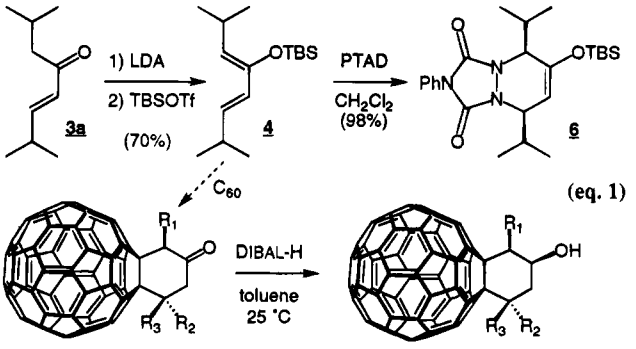
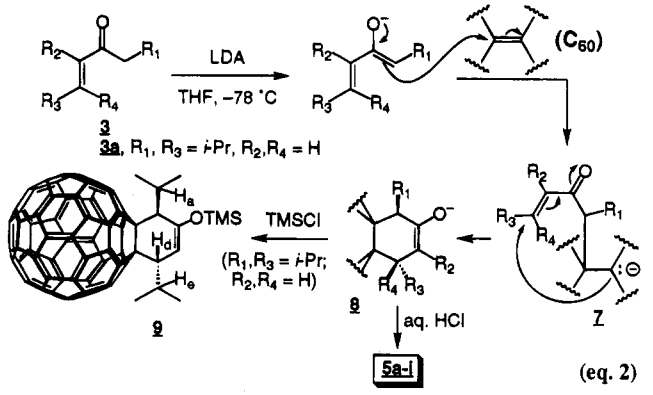
HIV-1 protease is an important target for antiviral therapy since it has a vital function in the maturation of the AIDS-inducing virus.[1] We have been interested in the preparation of C_{60}-based inhibitors of HIV-1 protease that show substantially higher binding affinity and specificity to this enzyme than that reported recently for a water-soluble methanofullerene, for which the fullerene moiety is the principal source of apolar binding interaction.[2] Two of the initial target molecules we have identified are diastereomeric alcohols **1** and **2**.[3] We report the successful preparation of alcohol **1** and a very convenient method to access sterically crowded C_{60} derivatives.



5a, R_1, R_2 = *i*-Pr, R_3 = H (*trans*) **1**, R_1, R_2 = *i*-Pr, R_3 = H (*cis, trans*; 80%)
5a', R_1, R_3 = *i*-Pr, R_2 = H (*cis*) **2**, R_1, R_3 = *i*-Pr, R_2 = H (*cis, cis*)

In the context of our Diels–Alder work with C_{60},[4] a logical way to assemble the framework embodied in **2**, where the *i*-Pr groups have *cis*-relationship, would be through a Diels–Alder reaction of 1*Z*,3*E*-diene **4** with C_{60} and subsequent reduction of ketone **5a'** (eq 1). However, we were aware of the steric bias imposed by the bulky *i*-Pr groups which could strongly disfavor the [4+2] cycloaddition with C_{60}. Diene **4** was assembled in three steps involving aldol condensation of isobutyraldehyde with 4-methyl-2-pentanone (LDA, THF, −78 °C) followed by dehydration to enone **3a** (CF_3CO_2H, CH_2Cl_2, reflux, 78%), and trapping the dienolate prepared from **3a** with TBS triflate (TBS = *tert*-butyldimethylsilyl; LDA, 70%). Heating C_{60} and diene **4** between 25–110 °C gave no reaction. However, the reaction of **4** with *N*-phenyl-1,2,4-triazoline-3,5-dione (PTAD) proceeded instantaneously at 0 °C to give adduct **6** in 98% yield. The *cis*-relationship of the *i*-Pr groups in **6** was verified through NOE difference experiments, confirming the correct stereochemical assignment of diene **4**.

We had to find an alternate method to functionalize C_{60} which would be amenable to sterically demanding groups at the 1,4-positions of the fused cyclohexane ring. Since C_{60} acts as an electron deficient olefin with a reactivity similar to α,β-unsaturated carbonyls,[5] it seemed likely that a dienolate anion, formed by α-deprotonation of an enone (**3**), would add in a Michael-like fashion to C_{60} to form an anionic intermediate (**7**) able to cyclize to an enolate (**8**) through an intramolecular Michael reaction, affording a ketone (**5a–i**) upon protonation (eq 2).[6] The formation of either diastereomer **5a** or **5a'** was not



deemed crucial since both diastereomeric alcohols **1** and **2** resulting from the reduction of the respective ketones were predicted to show significant increase in apolar binding to HIV-protease.[3,7]

Deprotonation of enone **3a** with LDA in THF and addition of the resulting dienolate to a solution of C_{60} in toluene maintained at −78 °C for 10 min proceeded smoothly to give the ketone **5a** in good yield as the only detectable diastereomer (Table 1). The *cis*- or *trans*-relationship of the *i*-Pr groups in **5a** could not be determined at first due to the lack of observable NOE effects.[8] However, the trimethylsilyl enol ether **9** was isolated in 43% yield next to ketone **5a** (41%) by quenching enolate **8** (R_1, R_3 = *i*-Pr; R_2, R_4 = H) with TMSCl (eq 2). The *trans*-stereochemistry of the *i*-Pr groups in **9** was demonstrated by the existence of diagnostic NOEs between H_d/H_a (6.5% enh) and H_d/H_e (14.4% enh). However, we had to determine if the slow acidic hydrolysis of silylenol ether **9** (THF, 1 M HCl, >3 h) gives the *trans*-diisopropyl ketone **5a** or its *cis*-diastereomer **5a'**, which could form by acid-catalyzed keto–enol tautomerization. This question was resolved by regenerating the enolate of ketone **5a** and trapping it under kinetic conditions (LDA, TMSCl, −78 °C, 35%). The resulting silyl enol ether was identical with compound **9**, confirming the *trans*-stereochemistry in diastereomer **5a**.

The reduction of ketone **5a** to alcohol **1** was successfully achieved with DIBAL-H in 80% yield (eq 1).[4] Alcohol **1** was expected to have a *cis*-relationship between its OH and the vicinal *i*-Pr group resulting from *anti*-attack of

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(2) Friedman, S. H.; Decamp, D. L.; Sijbesma, R. P.; Srdanov, G.; Wudl, F.; Kenyon, G. L. *J. Am. Chem. Soc.* **1993**, *115*, 6506–6509.
(3) Complexes were generated using DOCK, see ref 2. These were analyzed for increases in desolvation of hydrophobic surface (60–110 A^2) relative to Wudl's compound. Alcohols **1** and **2** were selected from ~40 substituted fullerenes; Friedman, S. H.; Rubin, Y.; Ganapathi, P. S.; Kenyon, G. L., manuscript in preparation.
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(6) Jung, M. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Ed.; Pergamon Press: New York, 1991; Vol. 4; pp 1–67.
(7) MM3, MacroModel 3.5, C. Still, Columbia University. Monte-Carlo searches led to the minimum energy conformations for **1** and **2**. Alcohol **1** had the two unique structures **1a** and **1b** (Figure 1) separated by 0.5 kcal mol^{-1}; alcohol **2** had a half-chair conformation (axial OH).
(8) Zhang, X. J.; Foote, C. S. *J. Org. Chem.* **1994**, *59*, 5235–5238.

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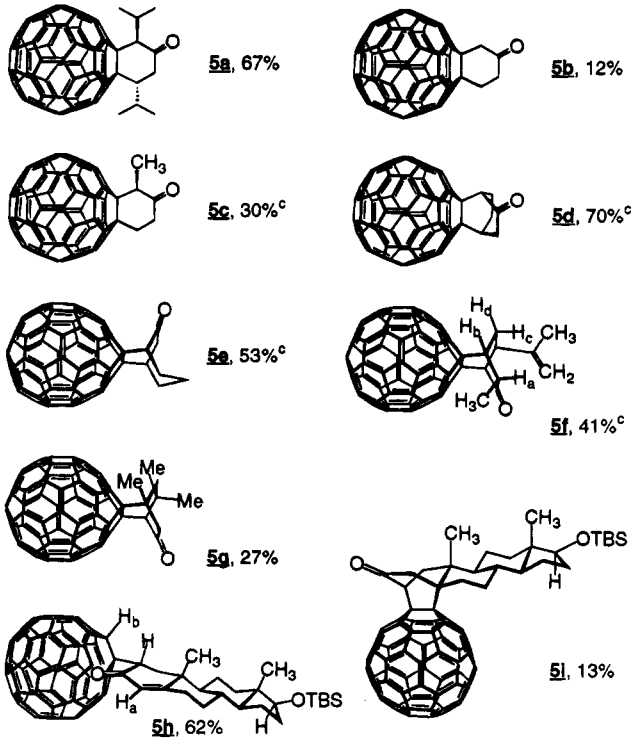
Table 1. Structures and Yields of the Ketones 5a–i[a,b]



[a] Yield based on recovered C_{60}. [b] Ketones **5a–i** and C_{60} separated by flash chromatography on SiO_2 with $PhCH_3$/CyH. [c] Yields for reactions run in presence of TMSCl.

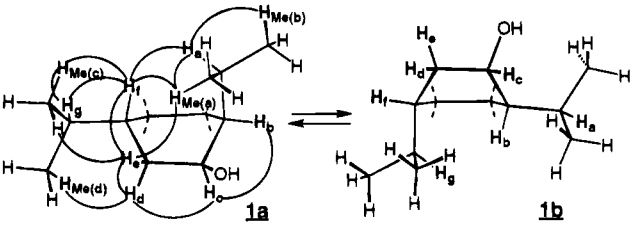


Figure 1. Correlations found in 2D NOESY and 2D T-ROESY experiments for alcohol **1** in its solution conformation **1a**.

the hydride reagent. Accordingly, the stereochemistry of alcohol **1** was confirmed from H–H coupling data obtained in $CDCl_3/CS_2$ and benzene-d_6/CS_2 (1:1) and from 2D NOESY and 2D T-ROESY[9] experiments. Both sets of 2D spectra showed key correlations between H_f and $H_a/H_{Me(a)}/H_{Me(c)}$ and between H_c and H_b/H_d, which taken with the H–H coupling data demonstrate that alcohol **1** exists as conformation **1a** in solution (Figure 1).[7]

Various enones were subjected to the dienolate addition to give mono and bicyclic ketones **5a–i** (Table 1). We found that performing most of these reactions at low molarity ($\sim 10^{-3}$ M) for a short time (2–4 min.) was crucial to avoid unwanted side reactions of the anionic intermediates. The reaction of methyl vinyl ketone with C_{60} gave cyclohexanone **5b**[4] in low yield, possibly due to the rapid polymerization of anions of type **7** or **8** by addition to the electrophilic core of C_{60}. Reaction of C_{60} with the more bulky ethyl vinyl ketone gave the methylcyclohexanone **5c** in significantly higher yield.[10]

Next, we applied this reaction to the construction of bicyclic frameworks fused to C_{60} since only few such systems have been prepared.[11] Reaction of C_{60} with the enolate of cyclopentenone gave only polymeric material. However, reactions involving substituted cyclohexenones and cycloheptenone proceeded very smoothly. Cyclohexenone afforded the crystalline bicyclo[2.2.2]octanone **5d** in very good yield. From the ^1H NMR spectrum of **5d** it was apparent that the three *endo* protons of the bicyclic framework are substantially deshielded by the fullerene system. Cycloheptenone afforded the bicyclo[3.2.2]-nonanone **5e** in reasonable yield.

The versatility of this reaction was examined with sterically demanding enones. Reaction of C_{60} with the enolate of (*R*)-(−)-carvone was highly stereoselective and furnished **5f** as a *single diastereomer*. The stereochemistry of the *exo*-isopropylene and *endo*-methyl substituents in **5f** was established through NOE experiments. Proton H_a showed 12% enhancement when proton H_c was irradiated and H_c showed 4.4% enhancement upon irradiation of H_a, in which case H_d showed no enhancement. The protons on the methyl group α to the carbonyl in **5f** are substantially deshielded (δ 1.91 ppm) and when irradiated only H_b showed an NOE enhancement (1.8%) besides H_a (3.7%). It is interesting to note that protonation of the intermediate enolate of type **8** proceeds only from the *exo* face, giving the least stable epimer with *endo*-methyl configuration. Reaction of C_{60} with isophorone gave the bridgehead-substituted bicyclo[2.2.2]octanone **5g** in modest yield.

The ultimate test of reactivity was performed with the hindered 17-TBS-testosterone. Upon addition of the corresponding enolate to C_{60}, the mono addition product **5h** was formed very rapidly. The ^1H NMR spectrum of **5h** shows H_a as a singlet at 6.24 ppm and H_b at 6.28 ppm as a broad signal reflecting a slow rotation around C_{60} or conformational exchange of the testosterone moiety. At 70 °C this latter peak sharpens indicating fast exchange. At −60 °C, two sets of isomers are observed in ~3:1 ratio which coalesce at −10 °C, giving a barrier of 12.0 ± 0.3 kcal mol^{-1}. We were able to obtain the fully cyclized ketone **5i** in addition to **5h** using a longer reaction time at 10 °C. However, when the reaction temperature was raised further, complete reversal of **5h**/**5i** to C_{60} occurred, indicating an equilibrium in the reaction pathway with progressive decomposition of the dienolate. The ^1H NMR spectrum of **5i** showed the absence of the enone proton and distinct downfield-shifted *endo* and less downfield-shifted *exo* protons on the testosterone framework.

We have established a remarkably facile method for the synthesis of sterically crowded fullerene derivatives. The availability of the target alcohol **1** allows us to test the inhibition of HIV-1 protease which will be reported in due course.

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Supplementary Material Available: Experimental section and ^1H and ^{13}C NMR spectra for compounds **1**, **4**, **5a–i**, **6**, and **9**; 2D NOESY or 2D T-ROESY spectra for **1** (35 pages).

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