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Efficient Asymmetric (2 + 2) Photocycloaddition Leading to Chiral Cyclobutanes. Application to the Total Synthesis of (–)-Grandisol

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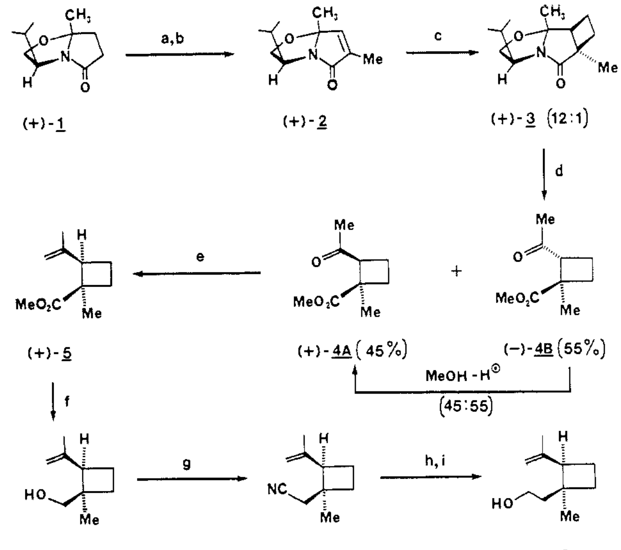
Although asymmetric thermal (2 + 2) cycloadditions have been extensively described,[1] photocycloadditions using two olefin components have been only reported in a few cases and lack general synthetic utility[2] as well as suffering from generally low yields. A number of (2 + 2) photocycloadditions, with high stereoselectivity, have been performed in an intramolecular fashion,[3] while others have elaborated chiral olefins in an intermolecular manner.[4] However, there are no reports, to our knowledge, of a synthetically useful (2 + 2) cycloaddition[5] using a "chiral enone" wherein the auxiliary directing the cycloaddition can be readily disconnected leaving only the chiral cyclobutane.[2a] We now report that this process has been successfully and efficiently implemented via the readily available bicyclic lactam **1**,[6] and as a demonstration of this efficient photocyclization, we have prepared (–)-grandisol **8** in nine steps. Treatment of (+)-**1** with *sec*-butyllithium, followed by methyl iodide, gave an 89% yield of the 2-methyl derivative as a 7:1 endo–exo mixture, which, without separation, was again metalated with *sec*-butyllithium and treated with diphenyl diselenide. The crude 2-(phenylseleno)-2-methyl lactam was oxidized according to Reich[7] to afford the α,β-unsaturated lactam **2** (70%, mp 46–47 °C $[\alpha]_D$ +41.3° (*c* 1, hexane)). This chiral enone was then subjected to photocycloaddition using ethylene in an apparatus described by Cargill[8] and furnished the cycloadduct **3** in 93% yield, containing 7–8%g of the *endo*-cyclobutane fused product. Pure **3** $[\alpha]_D$ +36.3° (*c* 1, hexane) was obtained by chromatography (ether–hexane, 1:1) but showed some instability during the separation. Therefore, the original photoaddition mixture (94:6 ± 1) was carried forward. It is of interest that the photocycloaddition of the simplest olefin proceeded with a fair degree of diastereoselectivity.[9] The important point to mention here is that the cycloaddition was performed on a chiral enone which can be detached due to its amide and aminal features. Thus, **3** was heated in 5% H_2SO_4–MeOH and produced the cyclobutane keto esters **4A,B** in 56% yield as a 45:55 mixture of epimers (Scheme I). It was found that the acetyl group epimerizes in the methanolic sulfuric solution by separating both[10] via radial chromatography and allowing pure **4B** to stir in H_2SO_4–MeOH for 12 h affording, once again, a 45:55 mixture of **4A,B**.

Scheme I[a]



[a] (a) 1.1 equiv *s*-BuiLi, of THF, –78 °C; 1.2 equiv MeI. (b) 1.1 equiv of *s*-BuLi, THF, –78 °C; 1.2 equiv of Ph_2Se_2, 2 h; 6.0 equiv of H_2O_2, pyridine, 3 h. (c) CH_2Cl_2 saturated with ethylene, 5 equiv of acetophenone, –78 °C, 1000-W Hg lamp, 5 h. (d) 5% H_2SO_4 in MeOH, 60 °C, 36 h. (e) 1.0 equiv of Ph_3PCH_3Br, 1.0 equiv of *n*-BuLi, THF, 25 °C, 2 h. (f) 1.0 equiv of Li AlH_4, THF, 8 h. (g) 2.0 equiv of TsCl, pyridine, 25 °C, 12 h; 2.0 equiv of NaCN, HMPA, 80 °C, 5 h. (h) 1.0 equiv of $(i\text{-Bu})_2AlH$, CH_2Cl_2, 25 °C, 3 h; 5% H_2SO_4. (i) 1.0 equiv of $LiAlH_4$, THF, 25 °C, 10 h.

This chiral cyclobutane synthesis was applied to the synthesis of grandisol **8**, the major component of the boll weevil pheromone,[11] by recognition of the fact that the adjacent absolute stereochemical centers correspond to those in **4A**.[12] Furthermore, the ability to epimerize **4B** to a 45:55 mixture of **4A,B** allows virtually complete utilization of the cyclobutane epimers toward the preparation of grandisol. In the event, **4A** was transformed into the isopropylidine derivative **5**[13] (80%, $[\alpha]_D$ +24:3° (*c* 1, hexane)) and the ester reduced to alcohol **6** (98%, $[\alpha]_D$ –8 ± 3° (*c* 1, hexane)). The one-carbon homologation to grandisol was accomplished by transforming alcohol **6** into the tosylate and reaction with sodium cyanide in HMPA[14] to give the nitrile **7**[15] (62%, $[\alpha]_D$ –20.3° (*c* 1, hexane)). Reduction with diisobutylaluminum hydride, followed by isolation of the aldehyde and reduction of the latter with lithium aluminum hydride gave (–)-grandisol (63% from **7**) which showed $[\alpha]_D$ –16 ± 2° (*c* 1, hexane), in good agreement with the values obtained by Magnus and Mori.[12] However, since the optical rotations are highly variable,[11] the Mosher ester[16] of (–)-grandisol was prepared and showed, when compared to racemic grandisol,[17] that (–)-grandisol was formed in a 94:6 ± 2 (88% ee) ratio. This correlates well with the 94:6 ratio of diastereomers present in the photoadduct **3**. Furthermore, the fact that the (–)-enantiomer of **8** was formed confirms the stereochemical assignment of the (2 + 2) photoaddition giving *exo*-**3** as the major diastereomer produced. Thus,

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(1) Paquette, L. A. In "Asymmetric Synthesis";, Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3.

(2) (a) Tolbert, L. M.; Ali, M. B. *J. Am. Chem. Soc.* **1982**, *104*, 1742. (b) Bernstein, J.; Green, B. S.; Rejito, M. *J. Am. Chem. Soc.* **1980**, *102*, 323. (c) Addadi, L.; Lahav, M. *J. Am. Chem. Soc.* **1978**, *100*, 2838.

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(5) For an excellent discussion of photochemical (2 + 2) cycloadditions, mainly of the Paterno–Buchi type, see: Schreiber, S. L. *Science* (*Washington, D.C.*) **1985**, *227*, 857.

(6) Meyers, A. I.; Wanner, K. T. *Tetrahedron Lett.* **1985**, *26*, 2047. The lactam is prepared from (*S*)-(+)-valinol and levulinic acid by azeotropic removal of water, 86%, $[\alpha]_D$ +95.48° (*c* 2, EtOH), +86.3° (*c* 1, hexane).

(7) Reich, H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*, 5434.

(8) Cargill, R. L.; Dalton, J. R.; Morton, G. H.; Caldwell, W. E. *Org. Synth.* **1984**, *62*, 118.

(9) Other olefins and various bicyclic lactams behaved similarly and the general method for reaching chiral cyclobutanes will be reported in due course.

(10) **4A**: oil, silica gel, ether–hexane; IR (neat) 1700, 1710 cm^{-1}; $[\alpha]_D$ +39.6° (*c* 1, hexane). **4B**: oil IR (neat) 1700, 1720 cm^{-1}; $[\alpha]_D$ –61.6° (*c* 1, hexane). Full spectral details are given in the supplementary material.

(11) Tumlinson, J. H.; Gueldner, R. C.; Hardee, D. D.; Thompson, A. C.; Hedin, P. A.; Minyard, J. P. *J. Org. Chem.* **1971**, *36*, 2616. The synthesis of racemic grandisol has been reported by a number of groups, cf.: Mori, K. In "The Total Synthesis of Natural Products; Wiley-Interscience: New York, 1981; Vol. 4.

(12) Optically active grandisol, (+) and (–), have been synthesized by: Hobbs, P. D.; Magnus, P. D. *J. Am. Chem. Soc.* **1976**, *98*, 4594. Mori, K. *Tetrahedron* **1978**, *34*, 915. These workers also confirmed the absolute configuration as 1*R*,2*S* for (+)-**8** and 1*S*,2*R* for (–)-**8**.

(13) Clark (Clark, R. D. *Synth. Commun.* **1979**, *9*, 325) has described racemic **5**.

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using (*S*)-(+)-valinol we were able to prepare (−)-grandisol meaning that utilization of (*R*)-(−)-valinol should lead to (+)-grandisol. This asymmetric methodology leading to chiral cyclobutanes is under active investigation.

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Supplementary Material Available: Isolation and complete physical data and NMR analysis using Mosher ester (7 pages). Ordering information is given on any current masthead page.

Self-Induced Nonequivalence in the Association of D- and L-Amino Acid Derivatives

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Consider enantiomerically enriched mixtures of chiral amino acid derivatives in achiral solvents. When the two enantiomers undergo diastereomeric solute–solute interactions to different extents, chiral differentiation of enantiomers may be possible without the aid of any foreign chiral substances since, by external comparison, each individual enantiomer can be in a different average environment.

In the present research, it was found that the enantiomeric *N*-acetylvaline *tert*-butyl ester (**1**)[1] exhibits self-induced NMR nonequivalence[2-4] through the formation of diastereomeric dimers interlinked via NH--O=C hydrogen bonds. Figure 1 illustrates two sets of amide NH proton doublets for D and L enantiomers recorded in a (0.1 M) CCl_4 solution at −20 °C. The intensity ratio of these signals was determined by the enantiomeric ratio in solution, indicating precisely that the associations occur under conditions of fast exchange. A similar chemical shift nonequivalence was also seen at higher sample temperatures as shown in Table I.

For a mixture of the enantiomers S_l and S_d, possible binary association equilibria are given as eq 1–3, where S_lS_l and S_dS_d

$$S_l + S_l \rightleftharpoons S_lS_l \tag{1}$$

$$S_l + S_d \rightleftharpoons S_lS_d \tag{2}$$

$$S_d + S_d \rightleftharpoons S_dS_d \tag{3}$$

are a homochiral dimer and S_lS_d a heterochiral dimer, respectively. When S_l is in large excess, S_l is associated primarily according to eq 1 and S_d according to eq 2. When the binary associations occur under conditions of fast interassociate exchange and a chemical shift of the sensor nuclei in the homochiral dimer is different from that in the heterochiral dimer, two NMR signals due to the enantiomers can be obtained, one corresponding to the weighted average of the three signals from S_l, S_lS_d, and S_lS_l and the other corresponding to the weighted average of the three signals from S_d, S_lS_d, and S_dS_d. Thus, the chemical shift nonequivalence ($\Delta\delta$) can be enhanced under conditions by which the enantiomeric purity of the enriched solute is enhanced. Decreasing the enantiomeric purity of the solute caused nonequivalent resonances to approach each other. In the 0.1 M racemic solution (C 0.5) in CCl_4, these resonances coalesced into one signal but with a chemical shift deviating by 0.051 ppm upfield from that of the corresponding L enantiomeric solution (homo shift).

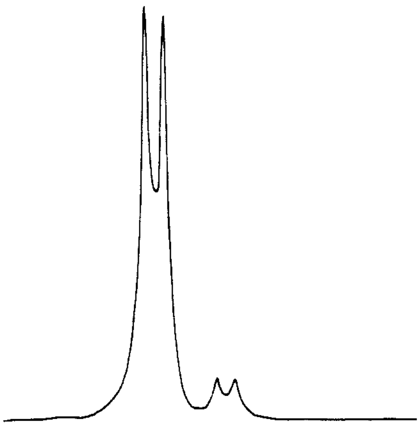

Figure 1. ^1H NMR spectrum of the amide NH group in the 1:9 mixture of D- and L-**1** (0.1 *M* solution in CCl_4) at −20 °C. The low-field doublet ($^3J_{HH}$ = 8.54 Hz, δ 6.725) and the small high-field doublet ($^3J_{HH}$ = 8.30 Hz, δ 6.566) were assigned to the L and D enantiomers, respectively, on the basis of an observed intensity ratio of 9:1.

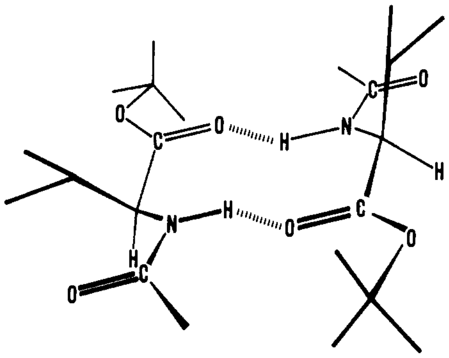

Figure 2. Proposed structure of the homochiral (L-L) dimer interlinked via bidentate NH--O=C ester hydrogen bonds.

A concentration study of ^1H and ^{13}C NMR in CCl_4 solution confirmed the involvement of the amide NH proton and each carbonyl carbon of both the ester and amide groups in hydrogen bond systems for both the pure enantiomer and racemic mixture. For the L enantiomer, the NH resonance shifted 0.38 ppm and the ^{13}C resonances for the two carbonyl carbons,[5] C=O amide and C=O ester, 0.43 and 0.22 ppm, respectively, upfield with dilution, in the concentration range 0.01–0.1 M (20 °C). Of the two carbonyl carbons, the resonance of the C=O ester carbon had a chemical shift difference between the racemic and L enantiomeric solution, similar to that observed for the amide NH resonance. In the 0.1 M racemic solution, the carbonyl ^{13}C resonance showed a weak but definite upfield shift of 0.05 ppm from that of the corresponding L enantiomeric solution. The chemical shift differences between the racemic and pure enantiomeric solution, observed in the resonances of the C=O ester carbon and that of the amide NH proton decreased with dilution in the above concentration region and finally disappeared at 0.01 M.

These results demonstrate that the association motifs of **1** contain two kinds of intermolecular hydrogen bonds: NH--O=C amide and NH--O=C ester. Of these two bonds, the sensor nuclei

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(1) *N*-Acetyl-L-valine *tert*-butyl ester, $[\alpha]^{18}_D$ −29.9° (*c* 1.00, ethanol) and its D enantiomer, $[\alpha]^{18}_D$ +29.6° (*c* 1.03, ethanol).

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(5) Two carbonyl carbons of the solute **1** were assigned by using a selective proton-decoupling technique in ^{13}C NMR. Chemical shifts determined for C=O amide and C=O ester carbons at 20 °C are 170.90 and 167.55 ppm, respectively, for the L enantiomer (0.1 M solution in CCl_4).

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