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Hydroxyacids as Efficient Chiral Spacers for Asymmetric Intramolecular [2+2] Photocycloadditions[1]

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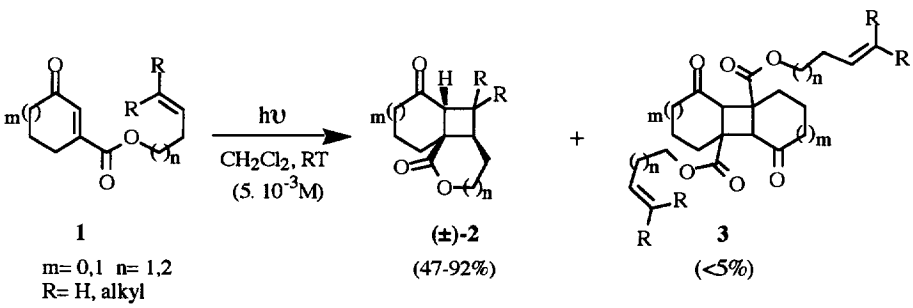
Abstract : An indirect and efficient enantioselective [2+2] photocycloaddition between 3-carboxycyclohex-2-enone and allyl alcohol, involving a three step sequence, is described. When the reagents are linked by covalent bonds to a chiral spacer such as L-lactic or (R)-3-hydroxybutyric acids, the corresponding photocycloadducts are isolated in high yields. with very high regio and diastereostereoselectivies. The reaction affords polyfunctional cyclobutanes as pure enantiomers.

Previous efforts to realize highly enantioselective [2+2] photocycloadditions of prochiral reagents, in solution and in the presence of chiral additives, have not yet been very successful.[2] Since the early attempts to control the configuration of all the new asymmetric centers created in the intramolecular [2+2] photocycloaddition of threitol bis-cinnamates,[3] numerous systems have been proposed for the diastereoselective preparation of cyclobutanic compounds.[4] However few of these methods can be considered satisfactory for enantioselective multistep syntheses. Furthermore and from the reported studies, it seems difficult to control simultaneously the regio-, the diastereo- and (or) even the enantioselectivity of the addition process.

We have previously described the [2+2] intramolecular photocycloadditions of ω-unsaturated derivatives of 3-carboxycycloalk-2-enones. Performed in methylene chloride or acetonitrile, irradiations at 366 nm of oxoesters **1** lead efficiently to only one cycloadduct **2**, in a racemic form, among all the possible regio- and diastereoisomers (Scheme 1).[5] Only small amounts of **3** (<5%), resulting from the dimerization of the cycloalk-2-enone chromophore were isolated. However, the reaction was shown to be very sensitive to the conformational restrictions introduced by the ethylenic linkage and medium ring cycles could be also formed during the cycloaddition process.[6]



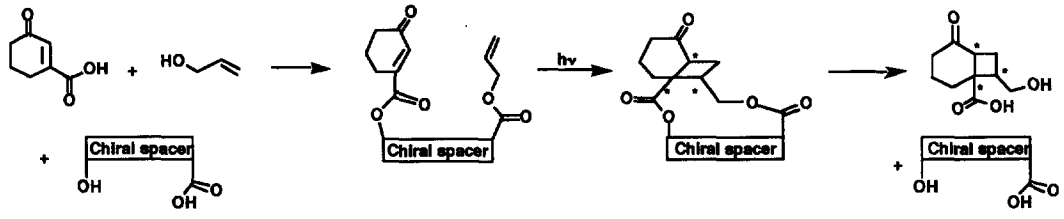
1
m= 0,1 n= 1,2
R= H, alkyl

(±)-2
(47-92%)

3
(<5%)

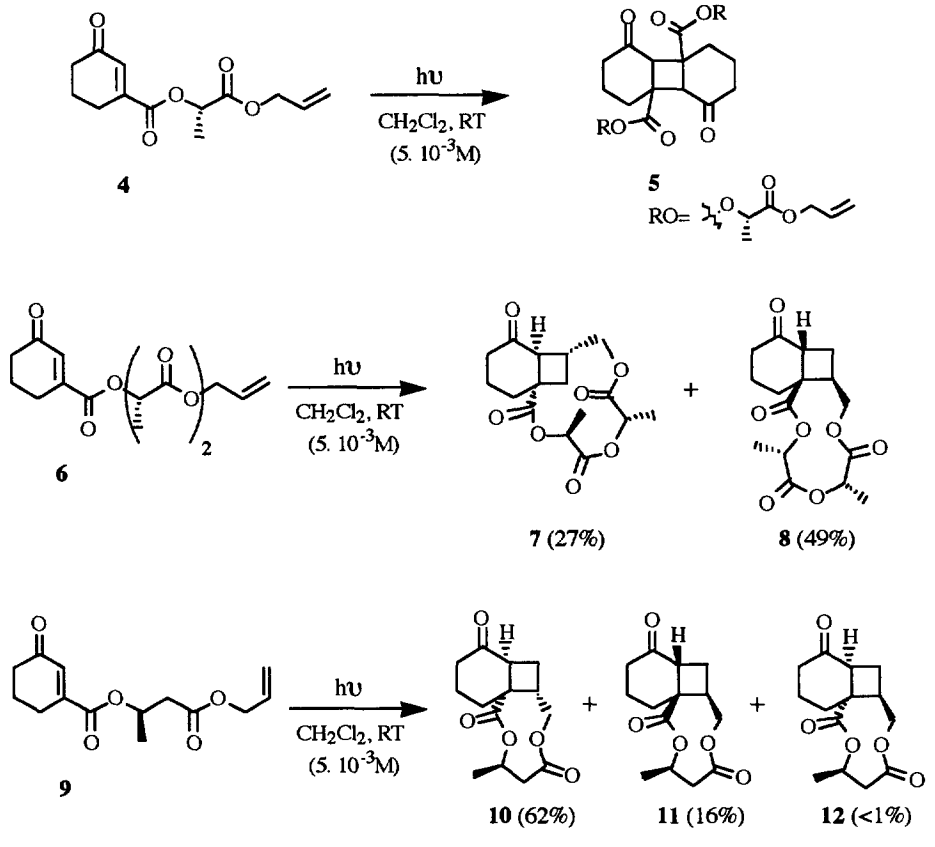
Scheme 1

We anticipated that it might be possible to take advantage of such conformational restrictions, introduced by ester groups, to induce a regioselective reaction and to control the configuration of all the new asymmetric centers, in the cycloaddition process. An indirect enantioselective cycloaddition involving a three step sequence and recovering of the chiral auxiliary should be possible and we decided to study the photocycloaddition of 3-carboxycyclohex-2-enone and unsaturated alcohols separated by a chiral spacer as indicated in Scheme 2.



Scheme 2

We now report that such an approach gives satisfactory results when quite inexpensive chiral reagents such as (S)-lactic acid or (R)-3-hydroxybutyric acid are used as the chiral spacer and the main and preliminary results are summarized in Scheme 3.



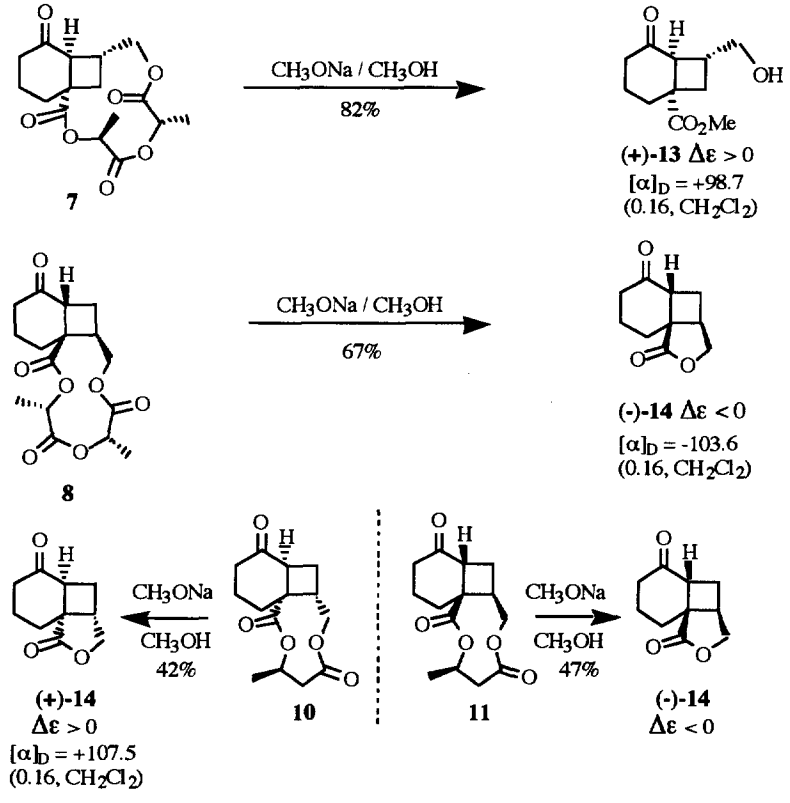
Scheme 3

No intramolecular photocycloaddition could be observed, during the irradiation of the lactic derivative **4**. Due to conformational restrictions induced by the two ester groups, the ethylenic bond is probably placed too far from the excited enone to allow an intramolecular photocycloaddition. However, the competitive intermolecular process occured and led to the formation of dimer **5** as the sole isolable product[7] (25%).

During the synthesis of **4**[6], we observed the competitive formation of esters such as **6**, having two lactic units in the spacer, resulting from an easy and well known dimerisation of lactic acid.[8] When **6** was irradiated at room temperature, in CH_2Cl_2, only two new compounds **7** and **8** could be isolated in 27% and 49% respectively. According to spectroscopic data,[9] structures of "straight" and "crossed" cycloadduct were assigned to **7** and **8** which result from an opposite regiochemistry in the addition process.

In contrast with the lactic derivatives, ester **9**, having a 3-hydroxybutyric acid unit as the chiral spacer and irradiated in similar conditions, led to cycloadducts **10** (62%), **11** (16%) and **12** (<1%), involving only one regiochemical approach of the ethylenic bond toward the enone moiety.

To prove the structure of the different cycloadducts and to try to determine the absolute configuration of the new asymmetric centers, we carried out their transformation by sodium methoxide in methanol according to scheme 4 and examined the circular dichroism of the products thus obtained. Thanks to the octant's rule[10] and by comparison with previous work in the literature[11], we were able to assign the absolute stereochemistry as depicted below.



Scheme 4

It appears that fused lactones of opposite configuration **(-)-14** and **(+)-14** are formed starting respectively from (S)-lactic and (R)-3-hydroxybutyric acid derivatives.

In conclusion, we have shown that chiral spacers such as L-lactic or (R)-3-hydroxybutyric acids placed between the two chromophoric moieties allow high regio and diastereoselective [2+2] photocycloaddition process. After separation of the adducts and alkaline hydrolysis of the chiral template, cyclobutane derivatives can be isolated in pure enantiomeric form. In order to improve the selectivities and to generalize the process, other chiral hydroxyacids and different alkenyl chains are currently tested.

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7) *Typical data:* **5**. NMR ^{1}H (250MHz, $CDCl_3$): 1.17 (6H, s); 1.58 (6H, d, 6.8Hz), 2.31 (2H, d, 16.7Hz), 2.65 (2H, d, 16.7 Hz), 3.67 (2H, s), 4.65 (4H, d, 5.7Hz), 5.24 (2H, q, 6.8Hz), 5.20-5.40 (4H, m), 5.90 (2H, ddt, 17.1, 10.3 and 5.7Hz). NMR ^{13}C (75MHz, $CDCl_3$): 17.1, 25.8, 29.5, 42.1, 49.1, 65.8, 69.9, 77.8, 80.7, 118.9, 131.4, 168.8, 169.7, 203.6. MS: 565 ($M^{+\cdot}$ +1, 40).

8) Ajioka, M., Enomoto, K., Suzuki, K., Yamaguchi, A. *Bull. Chem. Soc. Jpn* **1995**, *68*, 2125-2131.

9) *Selected data:*

7. NMR ^{1}H (250MHz, $CDCl_3$): 1.54 (3H, d, 7.2Hz), 1.70-2.25 (4H, m), 2.26-2.48 (2H, m), 2.50-2.65 (3H, m), 3.42 (1H, d, 2.6Hz), 4.06 (1H, d, 11.0Hz), 4.30 (1H, dd, 11.0 and 2.3Hz). NMR ^{13}C (75MHz, $CDCl_3$): 15.8, 16.7, 20.0, 30.8, 31.3, 34.0, 40.0, 45.6, 48.0, 66.8, 69.8, 71.7, 169.2, 169.9, 176.5, 212.4. IR ($CHCl_3$): υ (cm^{-1}): 1755, 1705. MS: 324 ($M^{+\cdot}$, 17).

8. NMR ^{1}H (250MHz, $CDCl_3$): 1.53 (3H, d, 7.2Hz), 1.58 (3H, d, 6.8Hz), 1.65-2.20 (4H, m), 2.25-2.50 (3H, m), 2.55-2.70 (2H, m), 3.66 (1H, t, 10.0 Hz), 3.96 (1H, dd, 11.2 and 12.4Hz), 4.45 (1H, dd, 11.2, 5.5Hz), 5.22 (1H, q, 6.8Hz), 5.40 (1H, q, 7.2Hz). NMR ^{13}C (75MHz, $CDCl_3$): 15.4, 16.0, 20.8, 23.1, 29.3, 37.8, 37.8, 41.3, 42.5, 49.1, 63.6, 69.7, 71.3, 168.8, 172.6, 210.7. IR ($CHCl_3$): υ (cm^{-1}): 1745, 1705. MS: 324 ($M^{+\cdot}$, 16).

13. NMR ^{1}H (250MHz, $CDCl_3$): 1.60-1.80 (1H, sl), 1.75-2.15 (4H, m), 2.15-2.30 (2H, m), 2.35-2.50 (2H, m), 2.56 (1H, ddt, 8.7, 6.1 and 2.6Hz), 3.15 (1H, d, 8.7Hz), 3.67 (2H, d, 6.1Hz), 3.72 (3H, s). IR ($CHCl_3$): υ (cm^{-1}): 1730, 1695.

14. NMR ^{1}H (250MHz, $CDCl_3$): 1.60-2.10 (3H, m), 2.10-2.60 (5H, m), 2.83 (1H, dd, 10 and 4.0 Hz), 2.94 (1H, dd, 9.5 and 1.1 Hz), 4.30 (1H, dd, 9.5 and 6.0 Hz). NMR ^{13}C (75MHz, $CDCl_3$): 22.2, 27.1, 27.4, 36.9, 40.4, 44.9, 51.0, 71.8, 180.6, 210.7. IR ($CHCl_3$): υ (cm^{-1}): 1768, 1705. MS: 181 ($M^{+\cdot}$+1, 15).

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