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Enantioselective Photocycloaddition Mediated by Chiral Brønsted Acids: Asymmetric Synthesis of the Rocaglamides

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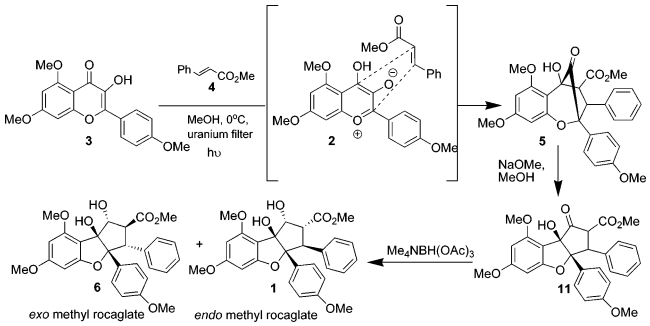
The genus *Aglaia* is the source of the rocaglamides, a unique group of natural products featuring a cyclopenta[b]tetrahydrobenzofuran skeleton.[1] We recently reported the synthesis of (±)-methyl rocaglate **1** using [3 + 2] dipolar cycloaddition of an oxidopyrylium betaine **2** derived from excited state intramolecular proton transfer (ESIPT)[2] of 3-hydroxyflavone (3-HF) **3** and methyl cinnamate **4**. The resulting cycloadduct **5** was transformed to methyl rocaglate **1** and stereoisomer **6** employing a base-mediated α-ketol rearrangement/hydroxyl-directed reduction sequence (Scheme 1).[3]

Scheme 1. Synthesis of (±)-Methyl Rocaglate



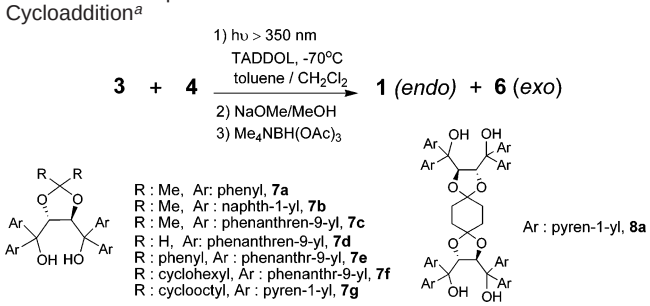
Herein, we wish to report an asymmetric synthesis of methyl rocaglate employing enantioselective [3 + 2] photocycloaddition mediated by functionalized TADDOL derivatives.

During our studies toward the synthesis of (±)-methyl rocaglate,[3] we found that the cycloaddition required polar protic solvents, such as methanol, in order to proceed. It has been proposed that ESIPT may be enhanced in such solvents due to the formation of solvated complexes involving "double proton transfer".[4] To access chiral, nonracemic methyl rocaglate, we therefore investigated use of chiral Brønsted acids[5] in aprotic solvents as host−guest[6] complexes to mediate photochemical cycloaddition. After screening a number of hydrogen-bonding additives, we identified TADDOL[5] reagents as chiral mediators (Table 1). For example, photochemical cycloaddition of **3** with methyl cinnamate **4** (5 equiv) using 1-phenyl TADDOL **7a** (1 equiv) in toluene at 0 °C afforded a 24% overall yield and 7% ee of (−)-methyl rocaglate **1** after ketol shift and reduction (entry 2).[7] Use of naphthyl TADDOL derivative **7b** led to an increase in enantiomeric excess to 25% (cf. entries 2 and 3). Investigation of reaction temperature showed noticeable effects on the enantioselectivity of the cycloaddition (cf. entries 2 and 4, and 3 and 5). On the basis of optical rotation data, use of TADDOL derivatives derived from L-tartrate was shown to favor the natural (−)-enantiomer of **1**.

Encouraged by these results, we proceeded to evaluate additional TADDOL derivatives in the photochemical cycloaddition (Table 1) at low temperature using a mixed solvent system (2:1 $PhCH_3$:CH_2Cl_2) to avoid low viscosity and poor substrate solubility. During our investigations, we found that the nature of both the aryl substituent and ketal side chain were important for high enantioselectivity. For example, use of additive **7f** bearing a 9-phenanthrenyl substituent and cyclohexyl ketal (entry 9) afforded **1** in 71% ee (53% overall yield). The highest enantioselectivity was achieved using dimeric TADDOL **8a** (89% ee, entry 12) but with low conversion. Fortunately, recrystallization of **1** obtained from TADDOL **7g** led to the formation of centrosymmetric racemate[8] crystals and the isolation of **1** (94% ee, 86% recovery) from the mother liquor. The TADDOL complexing agent could be recovered in high yield by precipitation from methanol. A control experiment involving addition of **7f** and 5 equiv of methanol (entry 10) led to a loss of enantioselectivity presumably due to achiral background reactions promoted by the protic cosolvent.[9]

Unexpectedly, when diphenyl (**7e**, entry 8) TADDOL acetal was employed as additive, methyl rocaglates **1** and **6** were obtained as racemates. X-ray crystal structure analysis of **7e** showed the presence of a TADDOL conformer[10] involving intramolecular H-bonding between the hydroxyl groups and the π system of the

Table 1. Development of Enantioselective Photochemical Cycloaddition[a]



entry	additive	yield of **5**, %[b]	yield of **1/6**, %[c]	ee of **1/6**, %[d]
1		32	45/19	racemic
2[e]	**7a**	60	41/15	7/5
3[e]	**7b**	61	49/7	25/18
4	**7a**	51	35/4	15/7
5	**7b**	92	52/9	40/36
6	**7c**	90	71/14	60/58
7	**7d**	70	69/14	25/22
8	**7e**	54	72/22	racemic
9	**7f**	79	67/19	71/51
10[f]	**7f**	73	47/9	53/30
11	**7g**	58	61/16	82/68
12	**8a**	22	52/7	89/78

[a] Reactions conducted with 1 equiv of 3-HF, 1 equiv of additive, and 5 equiv of methyl cinnamate in toluene/CH_2Cl_2 (2/1) at −70 °C for 12 h. [b] Isolated yield. [c] Isolated yield for the α-ketol rearrangement/reduction sequence. [d] Determined by chiral HPLC (see the Supporting Information). [e] Reaction conducted at 0 °C in toluene. [f] Reaction conducted in the presence of anhydrous CH_3OH (5 equiv).

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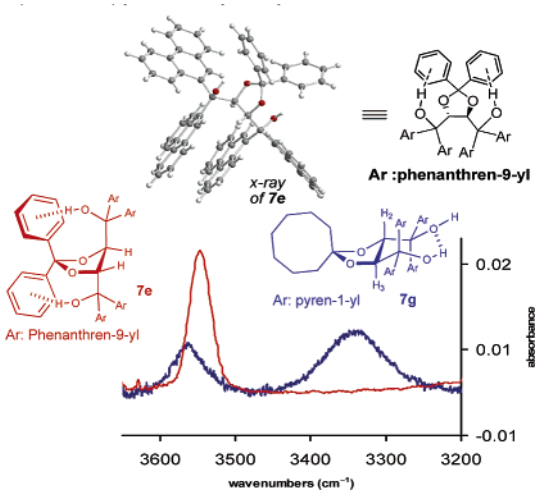


Figure 1. Alternate TADDOL conformers determined by infrared spectroscopy and X-ray analysis.

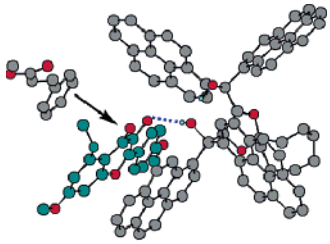


Figure 2. Proposed arrangement for enantioselective photocycloaddition.

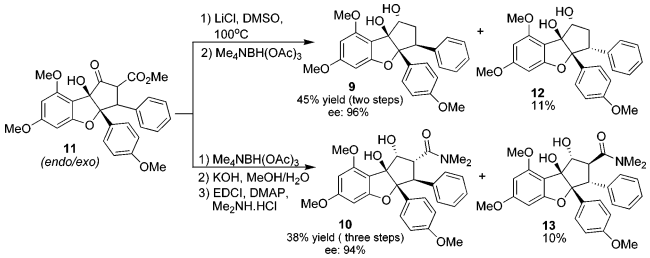
phenanthrene ring. The relevance of this conformer in solution was further confirmed by infrared spectroscopy (Figure 1), in which the hydroxyl stretching frequencies corresponding to intramolecular hydrogen bonding between the two hydroxyl[11] groups (additive **7g**) are red-shifted in comparison to frequencies for the weakly hydrogen-bonded additive **7e**.

To explain the enantioselectivity observed in the [3 + 2] photocycloaddition, we propose an assembly involving oxidopyrylium **2** and TADDOL **7g** (Figure 2). The well-defined arrangement of TADDOL may form a hydrogen bond with the oxidopyrylium via its free hydroxyl group, which may stabilizes the dipole.[8] A computational study (B3LYP/6-31+G*)[9] of the oxidopyrylium intermediate indicates a high degree of electron density on the phenoxide oxygen, suggesting this site as a strong point of interaction for hydrogen bonding. The stereofacial approach of the dipolarophile may be controlled by shielding of the aryl group at the pseudoequatorial position of the seven-membered ring formed by an intramolecular H-bond between the two hydroxyl groups.[5b]

Using the optimized conditions for enantioselective photocycloaddition (entry 11), we achieved the synthesis of the natural products rocaglaol **9** and rocaglamide **10**[1c] (Scheme 2). By using **4** as dipolarophile and **7g** as additive, we obtained rocaglaol[12] **9** in 96% ee after decarboxylation[13] and reduction of intermediate **11**.[9] Rocaglamide **10** could also be accessed from **11** via reduction, hydrolysis, and amide bond formation (94% ee).

In conclusion, we have developed an enantioselective synthesis of the rocaglamides and related natural products. The key strategy involves enantioselective dipolar cycloaddition of an oxidopyrylium species derived from excited state intramolecular proton transfer of 3-hydroxyflavones using specifically functionalized TADDOL derivatives as chiral Brønsted acids. Further applications of the

Scheme 2. Enantioselective Syntheses of Rocaglamide and Rocaglaol



photocycloaddition process and synthesis of other rocaglamide derivatives are currently in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF), including X-ray crystal structure coordinates and files in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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