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Regioselective α-Addition of Deconjugated Butenolides: Enantioselective Synthesis of Dihydrocoumarins

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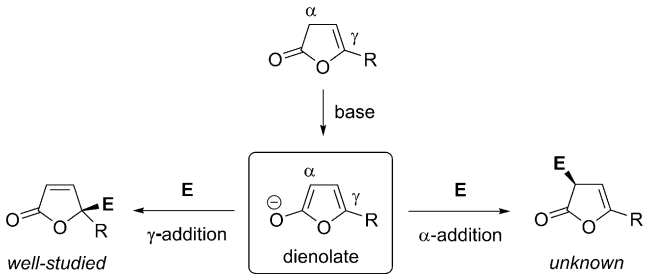
Abstract: *The enantioselective α-addition of deconjugated butenolides has rarely been exploited, in contrast to the well-studied γ-addition of deconjugated butenolides. In this study, an unprecedented asymmetric α-addition/transesterification of deconjugated butenolides with ortho-quinone methides generated in situ afforded a series of functionalized 3,4-dihydrocoumarins containing two contiguous stereogenic centers with excellent diastereo- and enantioselectivity. DFT calculations suggested that the rarely observed regioselectivity was due to the distortion energy that resulted from the interaction between the nucleophilic dienolate and the electrophilic ortho-quinone methide.*



Scheme 1. Regioselectivity in asymmetric addition reactions of deconjugated butenolides.

Butenolide scaffolds are ubiquitous structural fragments in biologically active molecules, natural products, and synthetic drugs.[1] Owing to the prevalence and significance of butenolides, the development of streamlined strategies for the construction of optically active butenolide-containing compounds has attracted considerable attention.[2] Deconjugated butenolides have emerged as versatile synthons for the construction of butenolide derivatives. A base can deprotonate deconjugated butenolides to generate highly active dienolate intermediates, which could react with electrophiles at different positions to give products of γ- or α-addition (Scheme 1). Recently, great progress has been made in asymmetric γ-addition of γ-substituted deconjugated butenolides to afford γ,γ-disubstituted butenolides. Various transformations involving asymmetric allylic alkylation,[3] a vinylogous Mannich reaction,[4] and vinylogous Michael addition reactions[5] of γ-substituted deconjugated butenolides have been documented. In contrast to the well-studied γ-addition of deconjugated butenolides, α-addition reactions have been far less exploited.[6] In 2003, Egorova and Timofeeva reported the α-addition of deconjugated butenolides to α,β-unsaturated ketones to give the racemic α-addition products (with respect to the butenolide).[6b] To the best of our knowledge, the asymmetric α-addition of deconjugated butenolides is still unknown. Hence, the development of asymmetric α-addition reactions of deconjugated butenolides would diversify the asymmetric reaction types of deconjugated butenolides.

ortho-Quinone methides (*o*-QMs) are a pivotal class of highly reactive intermediates in both biological processes[7] and organic synthesis.[8] A range of catalytic asymmetric processes of *o*-QMs have been successfully developed on the basis of transition-metal catalysis and organocatalysis.[9–11] During our studies on the utilization of *o*-QMs,[12] we focused on bifunctional organocatalytic reactions of *o*-QMs generated in situ. We previously reported the bifunctional squaramide-catalyzed enantioselective annulation of *o*-QMs generated in situ with active methylene compounds bearing a cyano group.[12e,f] Considering that γ-substituted deconjugated butenolides have been widely employed as nucleophilic reagents in asymmetric organocatalytic addition reactions, we envisioned that the combination of γ-substituted deconjugated butenolides with *o*-QMs generated in situ could enable the synthesis of chiral O-containing heterocycles by an asymmetric annulation reaction.

The reaction of deconjugated butenolides with *o*-QMs can proceed through two possible pathways. According to previous reports,[3–6] the nucleophilic addition tends to occur at the γ-position of deconjugated butenolides. Subsequently, the negatively charged oxygen atom attacks the electron-deficient unsaturated lactone through Michael addition followed by protonation to afford a fused butyrolactone **5** (Scheme 2, path A). Another pathway is the α-addition of deconjugated butenolides with the *o*-QM generated in situ, followed by intermolecular transesterification to give 3,4-dihydrocoumarins **3** (Scheme 2, path B). Herein, we report an unprecedented α-addition/transesterification reaction of γ-substituted deconjugated butenolides with *o*-QMs generated in situ from 2-(1-tosylalkyl)phenols. This asymmetric annulation provided streamlined and enantioselective access to functionalized 3,4-dihydrocoumarins containing two contiguous tertiary stereogenic centers: an essential scaffold in various natural products and pharmaceutical molecules.[13] Additionally,

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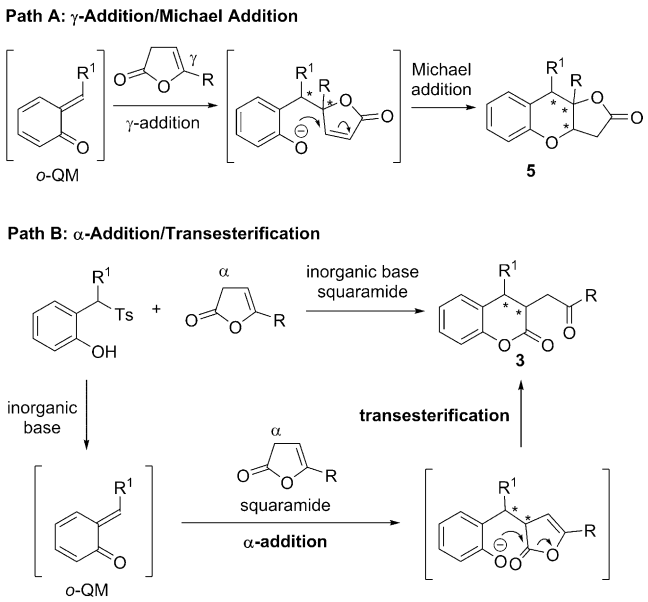


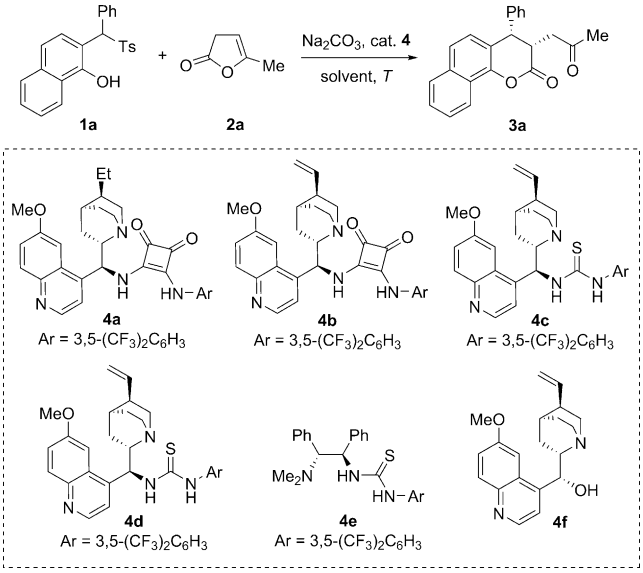
Scheme 2. Possible pathways for the asymmetric annulation of deconjugated butenolides with *o*-QMs.

theoretical studies based on DFT calculations provided important insight into the origin of the observed unusual regioselectivity.

To test the viability of our proposed protocol, we chose 2-(1-tosylalkyl)naphthol **1a** and α-angelica lactone (**2a**) as model substrates. This reaction was conducted under our previously reported reaction conditions.[12e] Pleasingly, the reaction proceeded smoothly to completion in 12 h, and 3,4-dihydrocoumarin **3a** containing two contiguous tertiary stereogenic centers was isolated in 97% yield with excellent enantioselectivity, albeit with moderate diastereoselectivity (3.9:1; Table 1, entry 1). Hence, the main challenge was to improve the diastereoselectivity. Various solvents were examined extensively, and it was found that the solvent had a crucial effect on the diastereoselectivity. Chloroform proved to be the most favorable solvent in view of enantioselectivity and diastereoselectivity (entries 2–5). Subsequently, a series of bifunctional organocatalysts were evaluated. Cinchona alkaloid based squaramide catalysts gave higher enantioselectivity and lower diastereoselectivity in comparison with thiourea catalysts. The quinine-based squaramide catalyst **4b** was the most efficient catalyst in overall terms (97% *ee*, d.r. 7.3:1; entries 6–10). Finally, the effect of the temperature was also explored. When the reaction temperature was decreased, the diastereoselectivity was improved slightly, and the enantioselectivity could be maintained with a longer reaction time. When the reaction was conducted with **4b** in chloroform at 30°C, the desired 3,4-dihydrocoumarin adduct was delivered with 97% *ee* and d.r. 9.2:1 (Table 1; entries 11–13).

After establishing optimal reaction conditions, we next sought to examine the scope and generality of the current α-addition/transesterification of *o*-QM precursors **1** with γ-substituted deconjugated butenolides **2**. For 2-(1-tosylalkyl)-naphthols **1a–j**, the electronic properties of the substituent on the aromatic ring R^1 had only marginal influence on the enantioselectivity and diastereoselectivity of the reaction.

Table 1: Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	*t* [h]	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	**4a**	*p*-xylene	12	97	3.9:1	91/78
2	**4a**	toluene	12	94	4.6:1	92/81
3	**4a**	benzene	24	97	4.9:1	93/81
4	**4a**	$CHCl_3$	18	94	6.2:1	96/82
5	**4a**	DCE	24	97	4.6:1	92/86
6	**4b**	$CHCl_3$	18	97	7.3:1	97/80
7	**4c**	$CHCl_3$	24	97	8.4:1	73/38
8	**4d**	$CHCl_3$	40	91	8.0:1	66/33
9	**4e**	$CHCl_3$	40	73	2.7:1	23/2
10	**4f**	$CHCl_3$	40	94	1.0:1	20/20
11[e]	**4b**	$CHCl_3$	60	97	8.3:1	97/75
12[f]	**4b**	$CHCl_3$	120	97	8.1:1	97/67
13[g]	**4b**	$CHCl_3$	144	97	9.2:1	97/69

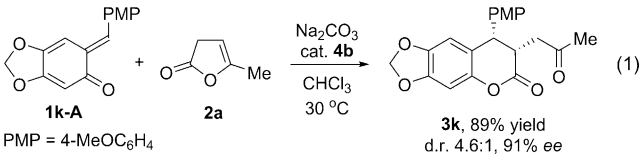
[a] Reaction conditions: **1a** (0.10 mmol), **2a** (0.12 mmol), **4** (0.01 mmol), Na_2CO_3 (0.12 mmol), solvent (1.5 mL), 60°C. [b] Yield of the isolated mixture of the two diastereoisomers. [c] The diastereomeric ratio was determined by ^{1}H NMR spectroscopy. [d] The *ee* value was determined by HPLC on a chiral stationary phase. [e] The reaction was carried out at 50°C. [f] The reaction was carried out at 40°C. [g] The reaction was carried out at 30°C. DCE = 1,2-dichloroethane.

However, possibly owing to steric hindrance, the presence of an *ortho* substituent on the aromatic ring resulted in a diminished d.r. value, and product **3d** was obtained with d.r. 6.2:1. The reaction of 2-(1-tosylalkyl)sesamol **1k** with α-angelica lactone delivered the desired product **3k** with good enantioselectivity and moderate diastereoselectivity. In the case of 5-methoxy-2-(phenyl(tosyl)methyl)phenol, the reaction gave the corresponding dihydrocoumarin **3l** with 89% *ee*, albeit with low diastereoselectivity and in moderate yield, when the reaction temperature was increased to 60°C. Unfortunately, when 2-(phenyl(tosyl)methyl)phenol was used as the substrate, none of the desired product was obtained; only a side product was obtained.[14] For 2-(1-tosylalkyl)phenols, electron-donating substituents on the phenolic ring were necessary for the reaction to proceed, possibly for stabilization of the *o*-QM intermediate.[9c,10f,11b,g,h] Furthermore, a series of deconjugated butenolides with different γ substituents were transformed successfully with

excellent enantioselectivity. Good diastereoselectivity was observed for γ-alkyl-substituted deconjugated butenolides, whereas the diastereoselectivity decreased for the corresponding γ-phenyl-substituted deconjugated butenolide. Finally, the annulation of 2-(1-tosylalkyl)naphthol **1a** with 5-(3-nitrophenyl)furan-2(3*H*)-one proceeded well with moderate diastereoselectivity to give **3q**. The absolute configuration of the product (+)-**3a** was unambiguously determined to be *S*,*S* by X-ray crystallographic analysis.[15]

We performed a control experiment to determine whether an *o*-QM intermediate was involved in the reaction. When the presynthesized stable *o*-QM intermediate **1k-A** was subjected to the standard conditions, the reaction proceeded successfully with good enantioselectivity and moderate diastereoselectivity [Eq. (1)]. This result is in accordance with the annulation of the 2-(1-tosylalkyl)sesamol substrate **1k** and α-angelica lactone **2a** (Scheme 3).

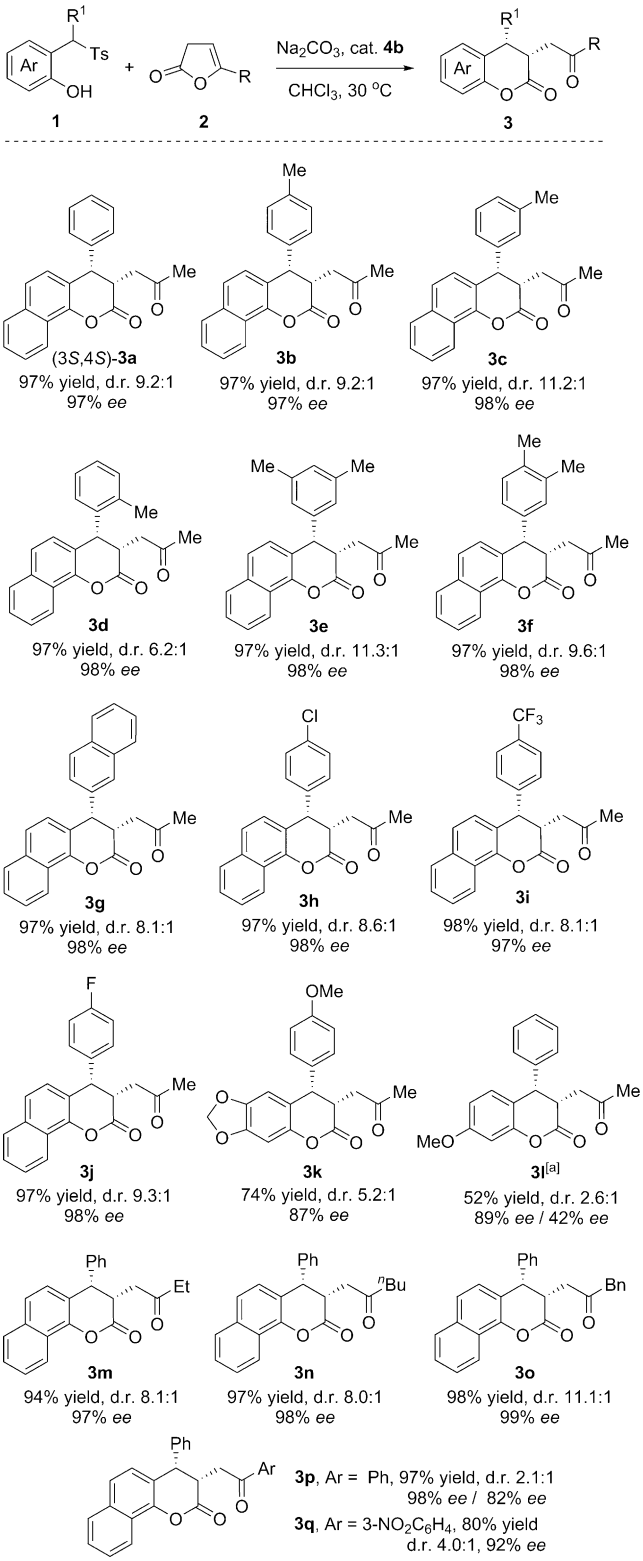
To properly understand the origin of the observed unprecedented regioselectivity and enantioselectivity, we



1k-A **2a** **3k**, 89% yield, d.r. 4.6:1, 91% *ee* (1)

PMP = 4-MeOC$_6$H$_4$

carried out density functional theory (DFT) calculations. The full Gibbs free energy profiles of the annulation of 2-(1-tosylalkyl)naphthol **1a** with α-angelica lactone (**2a**) under the catalysis of quinine-based squaramide **4b** were calculated,[16] and the calculations suggested that the regioselectivity and enantioselectivity were determined by the nucleophilic-addition step. We therefore focused on this key step. The nucleophilic addition may take place by two reaction modes: α- and γ-addition. We located eight transition-state structures for α-addition and γ-addition to identify the most plausible reaction profile. When the relative free energies of all transition states for α-addition were compared, the transition state **11-ts-*SS*** was found to be optimal, with the lowest activation free energy of 2.1 kcal mol^{-1} (Figure 1a). When the nucleophilic addition occurs at the γ-position of α-angelica lactone (**2a**), transition state **21-ts-*SSR*** has the lowest activation free energy of 4.0 kcal mol^{-1} (Figure 1b). The calculated activation energy of **11-ts-*SS*** (α-addition) is 1.9 kcal mol^{-1} lower than that of **21-ts-*SSR*** (γ-addition), thus indicating that regioselective α-addition is favored, which is consistent with the experimental results. To gain more insight, we employed a distortion/interaction model, in which the activation energy is separated into distortion energy and interaction energy[17] ($\Delta E^{\neq}_{act} = \Delta E^{\neq}_{dist} + \Delta E^{\neq}_{int}$). The difference in interaction-energy terms ($\Delta E^{\neq}_{int}$) between **11-ts-*SS*** and **21-ts-*SSR*** is only 2.1 kcal mol^{-1}. However, the difference in distortion-energy terms ($\Delta E^{\neq}_{dist}$) between the two transition states is 4.6 kcal mol^{-1}, thus suggesting that distortion energy plays an important role in the observed regioselectivity. Furthermore, the C1-C2-C3-C4 dihedral angle in **11-ts-*SS*** is 15.2°, which is 10.7° smaller than that in **21-ts-*SSR***, thus correlating well with the distortion-energy difference between the two transition states. Therefore, the better conjugation in the 2-(1-tosylalkyl)naphthol moiety leads to



Scheme 3. Scope of the reaction. Reaction conditions: **1** (0.10 mmol), **2** (0.12 mmol), **4b** (0.01 mmol), Na_2CO_3 (0.12 mmol), $CHCl_3$ (1.5 mL), 30 °C. Yields are for the isolated mixture of the two diastereoisomers. [a] The reaction was carried out at 60 °C. Bn = benzyl.

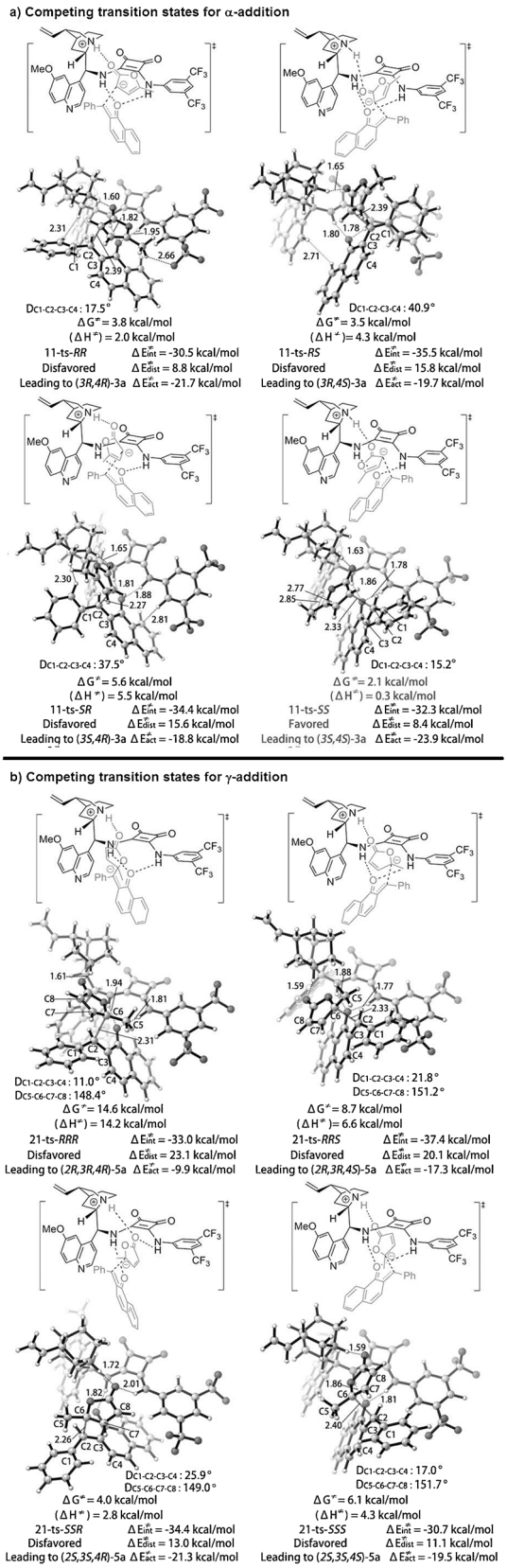


Figure 1. Competing transition states for α-addition and γ-addition.

a lower energy barrier in the α-addition step. Our calculated enantioselectivity for this reaction is also consistent with experimental observations.

In summary, we have developed an unprecedented enantioselective α-addition of deconjugated butenolides, as opposed to the well-studied asymmetric γ-addition of deconjugated butenolides. The asymmetric α-addition/transesterification of γ-substituted deconjugated butenolides with *ortho*-quinone methides that were generated in situ afforded a series of functionalized 3,4-dihydrocoumarins containing two contiguous stereogenic centers in high yields with excellent diastereo- and enantioselectivity. Theoretical studies based on DFT calculations revealed that the observed regioselectivity was due to the distortion energy that resulted from the interaction between the nucleophilic dienolate and the electrophilic *ortho*-quinone methide. Further efforts are currently under way toward the application of this methodology in organic synthesis.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · butenolides · dihydrocoumarins · nucleophilic addition · *ortho*-quinone methides

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[14] See the Supporting Information for details. When sodium carbonate was used as the base, the reaction did not occur. With potassium carbonate as the base, only a side product was obtained.

[15] CCDC 1450126 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[16] See Figure S1 in the Supporting Information for the full Gibbs free energy profiles of the reaction.

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Communications

Organocatalysis

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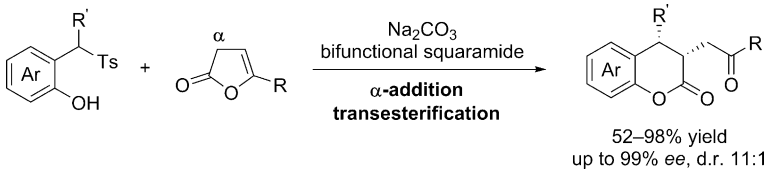
Regioselective α-Addition of Deconjugated Butenolides: Enantioselective Synthesis of Dihydrocoumarins



52–98% yield
up to 99% *ee*, d.r. 11:1

The alpha... but not the gamma: The α-addition of deconjugated butenolides has rarely been exploited, in contrast to their well-studied γ-addition. Now an unprecedented asymmetric α-addition/transesterification of deconjugated butenolides with *ortho*-quinone methides generated in situ from 2-(1-tosylalkyl)phenols has been developed for the synthesis of functionalized 3,4-dihydrocoumarins containing two contiguous stereogenic centers (see scheme).