Asymmetric Synthesis of an HIV Protease Inhibitor via a Novel α-Oxoketene/Ketene [4 + 2] Cycloaddition Reaction

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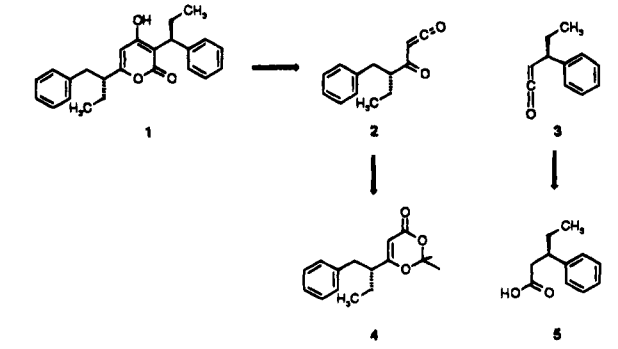
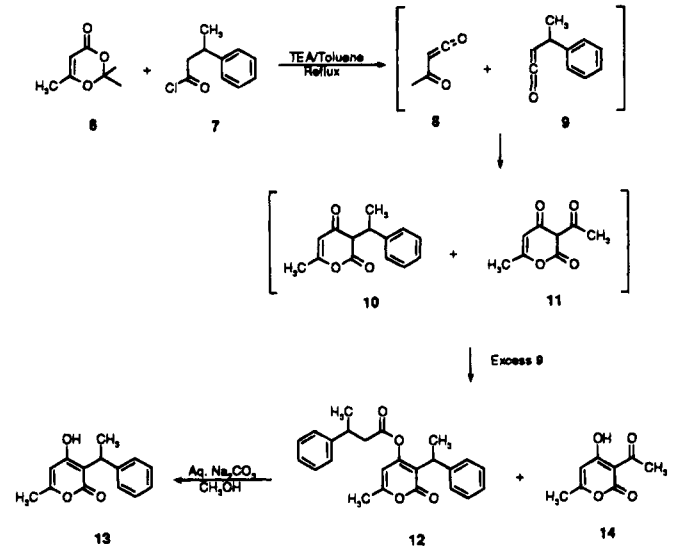
The 4-hydroxy-α-pyran-2-one template is found in a number of interesting natural and synthetic products,[1a] some of which are currently of interest as HIV protease inhibitors.[1b] While there are numerous methods available for the synthesis of the α-pyrone ring system,[1a,2] we recently found ourselves in the position of requiring an asymmetric synthesis of the 3(*S*),6(*R*)-disubstituted α-pyrone **1**. Racemic **1** is currently in phase I clinical trials. We envisioned the construction of **1** as arising from a remarkable cycloaddition reaction between a chiral α-oxoketene (**2**) and a chiral monosubstituted ketene (**3**) to yield the α-pyrone template.[3] Such a strategy should yield the α-pyrone nucleus, in which the chirality on both the C-3 and C-6 substituents is readily secured. We imagined the chiral ketene as arising via asymmetric Michael methodology to secure the dihydrocinnamic acid derivative (**5**) (Scheme 1).[4] It was anticipated that the chiral α-oxoketene, generated thermally from an appropriate dioxinone precursor[5] (**4**), could be prepared utilizing Evan's asymmetric alkylation methodology[6] with subsequent homologation[7] and dioxinone formation.[5] In addition to the availability of each chiral (or achiral) component, the generality of this strategy would also facilitate the synthesis of other interesting and previously inaccessible structural modifications of the α-pyrone system. To test the above idea, we first examined the reaction between the α-oxoketene **8**[9] and ketene **9**. Both reactive partners were generated *in situ* by adding a mixture of commercially available dioxinone **6** (1 equiv) and triethyl amine (TEA; 2 equiv) to acid chloride **7** (2 equiv) in refluxing toluene (Scheme 2). The acetone generated from the cracking of the dioxinone was removed from the reaction by passing a stream of nitrogen over the reaction solution. The reaction was complete in 3 h and gave the desired α-pyrone **13** in 55−60% yield after basic hydrolysis of intermediate enol acetate **12**. Formation of **12** indicated that, under the reaction conditions, the α-pyrone produced in the reaction reacted faster with the available ketene than did the α-oxoketene.[10] Also isolated from the reaction was 5−10% of **14**, a result of dimerization of α-oxoketene **8**.[8]

We next examined the utility of this cycloaddition reaction in the asymmetric synthesis of **1**. The α-oxoketene component was prepared via alkylation of the lithium enolate of **15** with benzyl bromide[6] to afford **16** in 88% yield (Scheme 3). Hydrolysis[11] ($LiOH/H_2O_2$) then afforded the chiral acid **17** in 94% yield (>98% ee). Conversion of **17** to the corresponding acid chloride **18** and subsequent homologation with lithio-*tert*-butylacetate[7] yielded **19**. Treatment of **19** with H_2SO_4/Ac_2O/acetone afforded the 1,3-dioxin-4-one **4** in an overall yield of 70% (from **18**). Determination of the enantiomeric excess of **4** using a chiral shift reagent indicated >98% enantiomeric purity.[12] The required chiral acid chloride **20** was prepared from the known (*R*)-β-phenylpentanoic acid **5**[13] in quantitative yield ($SOCl_2/CH_2Cl_2$). Addition of a mixture of dioxinone **4** and TEA

Scheme 1



Scheme 2



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⊥ Physical and Analytical Chemistry.
|| Chemical and Biological Screening.

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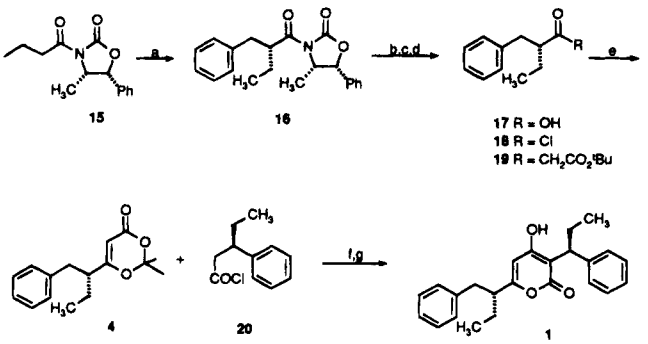
Scheme 3[a]



[a] (a) LDA/THF/BnBr; (b) $LiOH/H_2O_2$; (c) $(COCl)_2$; (d) lithio-*tert*-butylacetate; (e) acetone/H_2SO_4/Ac_2O; (f) TEA;toluene/reflux; (g) NaOH/CH_3OH.

(2 equiv) to a refluxing toluene solution of **20** followed by continued heating for 3 h afforded, after hydrolysis, the desired α-pyrone **1** in 78.5% yield. There was no evidence of dimer formation in this reaction. An HPLC[14] trace of the crude reaction product failed to show the presence of another diastereomer, indicating that the reaction had proceeded with absolute stereochemical control.

To provide some insight into the [4 + 2] cycloaddition reaction, a series of semiempirical AM1 calculations[15,16] were carried out on systems involving **8** and **9**. As shown in Figure 1, addition of the C=C and C=O ketene moieties of **9** across the C=C—C=O substructure of **8** yielded transition-state complexes **TS1** and **TS2**, respectively. Also illustrated in Figure 1 are structures **TS3** and **TS4** obtained in the dimerization reactions of **8**. In view of the fact that the AM1 reaction barriers reported in Table 1 are greatly exaggerated, small differences in the size of $\Delta H_f^{\ddagger}$ for the competitive cycloaddition reactions are probably not too significant, especially at high reaction temperature. However, the calculations suggest that barrier differences do favor the kinetics for dimerization of **8**, and this explains why an excess of **7** is required to drive the reaction toward the desired product **13**. The calculated values of $\Delta H_f^{\ddagger}$ reveal that the addition reactions are all extremely exothermic, but there are large differences in the stability of the cylic products. Ranked according to stability, the various cycloaddition products exhibit the following order: 10 > 11 ≫ 21 > 22. In the presence of Et_3NH^+, keto—enol transformation is expected to occur readily. The calculations reveal that the observed enol tautomers, **13** and **14**, are significantly more stable than the respective keto tautomers, **10** and **11**. Formation of **14** is strongly favored by an internal hydrogen bond between the 4-hydroxy and 3-acetyl substituents. On the other hand,

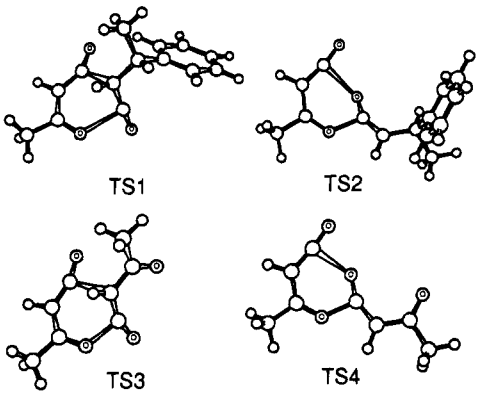
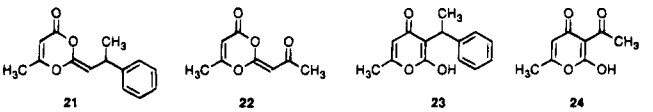


Figure 1. Transition-state complexes illustrating the concerted [4 + 2] cycloaddition reactions involving **8** and **9**. Using the numbering system for the α-pyrone ring to identify atoms, key distances of approach are as follows: O1···C2 = 2.233 Å and C3···C4 = 1.957 Å in **TS1**; O1···C2 = 1.772 Å and C3···C4 = 2.264 Å in **TS3**. With the atom numbering convention for the 1,3-dioxin ring system, the distances of approach are as follows: O1···C2 = 1.677 Å and O3···C4 = 2.233 Å in **TS2**; O1···C2 = 1.645 Å and O3···C4 = 2.271 Å in **TS4**.

Table 1. AM1[a] Heat of Reaction, ΔH_f, and Reaction Barrier, $\Delta H_f^{\ddagger}$, Calculated for Systems Involving α-Oxoketene **8** and Ketene **9**

reactant(s)	product[b]	ΔH_f (kcal/mol)	transition state	$\Delta H_f^{\ddagger}$ (kcal/mol)
8 + **9**	**10**	−38.2	TS1	18.5
8 + **9**	**21**	−21.1	TS2	17.7
10[c]	**13**	−4.1		
10[c]	**23**	6.5		
8 + **8**	**11**	−33.9	TS3	17.7
8 + **8**	**22**	−14.9	TS4	16.5
11[c]	**14**	−9.9		
11[c]	**24**	−1.6		

[a] Molecules and transition-state complexes were fully optimized using restricted Hartree—Fock calculations as implemented in the MOPAC 6.0 program.[17] Transition-state complexes were characterized by vibrational analysis, where only one normal mode exhibited an imaginary frequency corresponding to motion along the reaction coordinate. Relaxation of the transition-state geometry following a slight shift along the reaction coordinate led to formation of reactants or product depending on the direction of the perturbation. [b] The following molecules were not observed as reaction products:



[c] Acid-catalyzed keto → enol transformation.

the 2-hydroxy tautomers, **23** and **24**, are very unlikely high-energy structures.

In summary, the cycloaddition reaction between an α-oxoketene and a ketene is an extremely efficient method for the construction of substituted α-pyrones containing chiral appendages. We are continuing to explore the scope and mechanism of this new reaction.

(14) Chiralcel OD column in tandem with a Chiralcel OD-H column (trademarks of Daicel Chemical Industries, Ltd., Tokyo, Japan) with 97:3:0.2 (v/v) hexane/ethanol/glacial acetic acid.

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