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# Efficient Syntheses of a New Chiral Diene and a New Bridgehead Enone for a Diels-Alder Approach to Kaura-9(11)-16-dien-19-oic Acid

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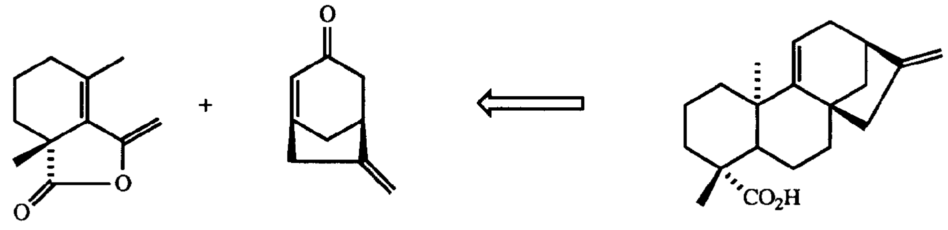
**Abstract**: Efficient syntheses of a new chiral diene and a new bridgehead enone for a Diels-Alder approach to kaura-9(11)-16-di-en-19-oic acid (**1**) are described.

In recent developments of the Diels-Alder reaction for natural product synthesis, two aspects have attracted considerable attention; namely, the use of chiral dienes containing an allylic heteroatom to control π-face-selectivity[1] and bridgehead enones as dienophiles[2] for the construction of complex polycyclic systems.

As a continuation of our interest in the synthesis of bioactive kaurane diterpenoids[3] we are engaged currently in the total synthesis of kaura-9(11)-16-dien-19-oic acid (**1**) which has been isolated from the Mexican medicinal plant Zoapatle (**Montanoa tomentosa**)[4] and possesses potent contragestational activity[5]. On the bases of our exploratory experiments[6], we designed a Diels-Alder approach to **1** (Scheme 1). This approach presents several interesting features: a rigid bicyclic system of chiral diene **2** in which the carboxyl group exists in a latent form as a γ-methylenebutyrolactone ring, is useful for both reactivity enhancement and asymmetric induction. In addition the approach utilises a highly reactive bicyclo-[3.2.1]-octene-3-one (**3**) as the dienophiles following work pioneered by House.[2a] Thus Scheme 1 presents a plausible highly convergent asymmetric route to **1**. We now report the synthesis of model diene **2a** and dienophile **3**.



(R)-(2) (3) (1)

Scheme 1

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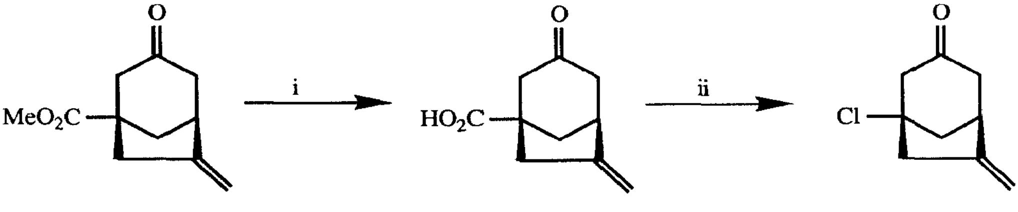
Due to the great reactivity and the instability of the bridgehead enone **3**, compound **3a** was chosen as its more stable latent form which could be readily transformed *in situ* to **3**[2] (Scheme 2). The key halodecarboxylation step for the conversion of **5**, obtained from **4**[7], to **3a** was accomplished by treatment of **5** with NCS and $Pb(OAc)_4$, to furnish an 82% yield of **3a**[8] after a short $SiO_2$ column filtration.



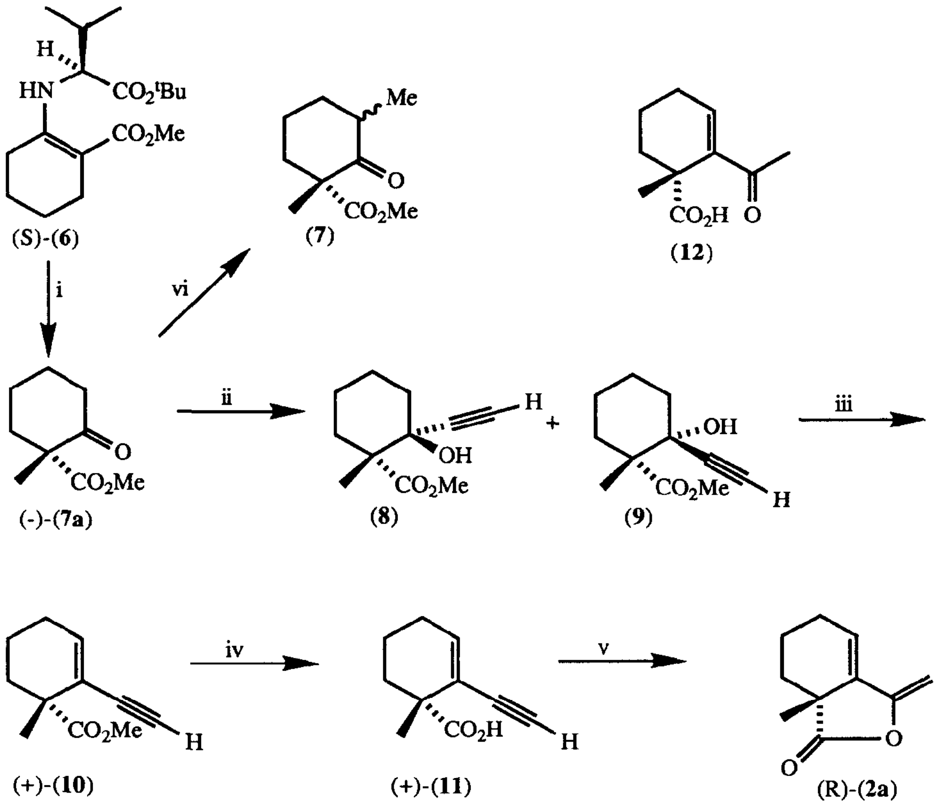
(4) (5) (3a)

Scheme 2:
Reagents and conditions: i) 4M LiOH, MeOH, $H_2O$, r.t., 100%;
ii) NCS/$Pb(OAc)_4$, DMF-HOAc, 45°C, 82%.

To study the reactivity and asymmetric induction of the new chiral diene (R)-**2** in the Diels-Alder reaction, (R)-**2a** was first prepared as model compound. A retrosynthetic analysis of chiral (R)-**2a** required the chiral β-keto ester (R)-**7a**[9] as the chiral precursor, which could be prepared in turn from the enamine (S)-**6** by Koga's elegant asymmetric methylation.[10] The synthesis of (R)-**2a** is depicted in Scheme 3.

Treatment of (-)-**7a** with ethynyl magnesium bromide yielded an inseparable diastereomeric mixture of ethynyl carbinols **8** and **9** (9:1) in nearly quantitative yield. Since the nucleophiles are known to attack preferentially from the axial side of cyclohexanones,[11] the major product **8** is presumed to have the hydroxy group in the equatorial position. Unfortunately, attempts to prepare diene (R)-**2a** *via* the enone acid (R)-**12**, prepared by Rupe rearrangement of **8** or **9** failed and an alternative route was employed to convert **8** and **9** to (R)-**2a**. Treatment of the diastereomeric mixture of **8** and **9** with $POCl_3$ in hot pyridine led to (+)-**10**, $\{[\alpha]_D^{20}$ +32.5 (c 0.85, $CHCl_3$)$\}$ in 71% yield. Hydrolysis of (+)-**10** gave crystalline (+)-**11**, mp. 71°C, $\{[\alpha]_D^{25}$ +40.3 (c 0.21 $CHCl_3$)$\}$ in 100% yield. Cyclization of acetylenic acid (+)-**11** was readily achieved on heating with a catalytic amount of silver carbonate[12] in benzene to give (R)-**2a**[8] in quantitative yield. For the synthesis of (R)-**2**, (-)-**7a** was methylated with MeI and a diastereomeric mixture of **7** was obtained. Thus, diene (R)-**2** could be prepared from the same reaction sequence as (R)-**2a** (Scheme 3).

Scheme 3 thus provides an easy access to both enantiomers of dienes **2** and **2a**. The reactivity and asymmetric induction of both dienes **2** and **2a** and dienophile **3a** for the Diels-Alder reaction are now being explored.



Scheme 3:
Reagents and conditions: i) ref. 10; ii) HCCMgBr, THF, -78°C, 100%; iii) $POCl_3$, Py, 90°C, 70%;
iv) 4MLiOH, MeOH, $H_2O$, r.t., 100%; v) $Ag_2CO_3$, $C_6H_6$, 80°C, 100%;
vi) LDA, THF-HMPA, -78°C, MeI.

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8. Spectral data of compound (R)-**2a**, MS (m/e relative intensity %): 164 ($M^{+\cdot}$ 58), 136(84), 135(60), 121(86), 108(31), 107(22), 93(77), 91(75), 79(100). $^1$H-NMR ($CDCl_3$, 200 MHz) 6.08 (t, J = 4.0 Hz, 1H), 4.68 (d, J = 2.5 Hz, 1H), 4.62 (d, J = 2.5 Hz, 1H), 1.25 - 2.35 (m,9H) ppm. **3a** IR(film) 1720(C=O)cm$^{-1}$; MS (m/e relative intensity,%): 172, 170 ($M^+$ +1,9,31), 136(33), 135(45), 107(30), 93(100), 92(98), 91(86) $^1$H-NMR ($CDCl_3$ 90 MHz) 5.00 (s,br,1H), 4.96 (s,br,1H), 3.07 - 2.78 (m,5H), 2.53 - 2.20 (m,4H) ppm.
9. e.e of (-)-(R)-**7a** was determined by the LIS-NMR technic [Eu(hfc)$_3$ in $C_6H_6$] as >95%. $[\alpha]_D^{21}$ -95 (c, 3.9, EtOH); Lit.[10] $[\alpha]_D$ -108 (EtOH), e.e. 99%.
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