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Short Communication

A novel approach to decalin synthons of bioactive terpenoids: Inverse electron demand Diels–Alder reactions†

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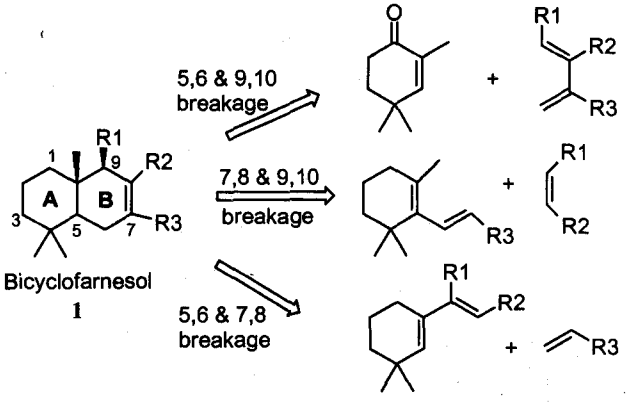
Abstract

A new approach to the synthesis of decalins and tricarbocyclic systems has been achieved through inverse electron demand Diels–Alder reaction.

Keywords: Synthesis, bicyclic terpenoids, inverse electron-demand Diels–Alder reaction.

The use of an additional functional group to enhance the activity of dienes or dienophiles while facilitating the incorporation of functionality into a specific position of adducts represents an important area of investigation on recent developments of Diels–Alder chemistry.[1] Development of new synthetic methods for the decalin systems by efficient routes is an interesting challenge.[2–7]

The retrosynthetic analysis of bicyclofarnesol nucleus (**1**) suggests that all the previous Diels–Alder approaches for ring B construction were based on the disconnection across C7–C8 and C9–C10, and C5–C6 and C9–C10 bonds. The present approach visualizes hitherto unexplored construction through the disconnection across C5–C6 and C7–C8 bonds. This approach



†Dedicated to Prof. S. C. Bhattacharyya.
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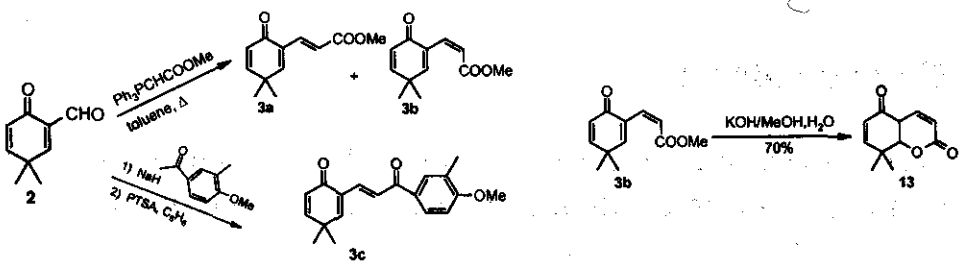
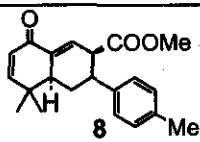
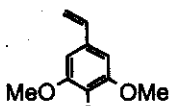
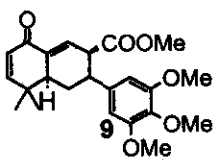
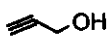
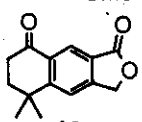
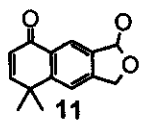
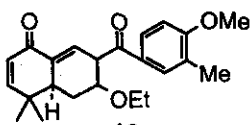


is based on inverse electron-demand Diels–Alder strategy, where the diene is an electron-deficient partner in the reaction.

Continuing our study on the synthesis of decalin systems,[8–11] we report herein a facile method for the cycloaddition reactions of methyl β-(5,5-dimethylcyclohexa-1,3-dien-1-yl) acrylate (**3a–b**) and chalcone (**3c**) with electron-rich dienophiles. The Wittig reaction of 2-formyl-4,4-dimethylcyclohexa-2,5-dien-1-one (**2**)[12] with stabilized ylide methoxycarbonyl-methylenetriphenylphosphorane[13] in refluxing toluene yielded an inseparable mixture of *cis*-

Table I
Diels–Alder reaction between 3a-c with electron-rich dienophiles

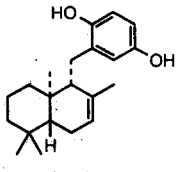
Diene	Dienophile	Temp. (°C)	Time (h)	Adduct	Yield
3a	 **4**	160	2	 **8**	55%
3a	 **5**	160	3	 **9**	58%
3a	 **6**	160	3	 **10**	20%
				 **11**	60%
3c	 **7**	160	3	 **12**	50%

and *trans*-dienes (**3a-b**; 20:80; 90%). Similarly, the chalcone (**3c**) was obtained by the reaction of aldehyde **2** with 3-methyl-4-methoxyacetophenone in the presence of base followed by dehydration with *p*-toluenesulfonic acid.

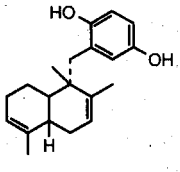
A mixture of diene (**3a–b**) (1 mole) was heated in a sealed tube with dienophiles (**4,5**) (2 mmol) and hydroquinone (10 mg) in toluene at 160–165°C for 2–3 h (Table I) followed by purification by silica gel chromatography furnished adducts **8–11** . Similarly, compound **12** was obtained from chalcone **3c** through reaction with methyl vinyl ether (**7**).

The paramount importance was the obtention of *endo* adducts with excellent regioselectivity. The structure and regiochemistry were confirmed by ^{1}H NMR studies.

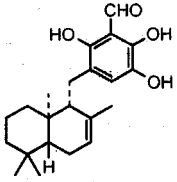
The reaction of the diene with propargyl alcohol undergoes tandem Diels–Alder reaction and cyclization to yield tricarbocyclic skeletons. Interestingly, similar tricarbocyclic systems are found in many natural products,[14] isolated from *Tanacetum fastigiata*,[15] sevasinolide sesquiterpene lactone from *Tanacetum densum* and *Vulgarin tauremisin*.[16] The adduct **12** is linear analogue of antiHIV, antitumour and antibacterial merosesquiterpenes, such as isozonarol (**14**),[17] avarol (**15**)[18] and siphonodictyol C (**16**).[19]



14 ISOZONAROL



15 AVAOL



16 SIPHONODICTYAL C

Thus the present method has the potential for the rapid assembly of decalin skeleton of a number of other natural products.

2. Experimental

2.1. *Preparation of diene 3a-b*

A mixture of compound **2** (2 g, 13.33 mmol) and methoxycarbonylmethylenetriphenylphosphorane (6.6 g, 20 mmol) in toluene (20 ml) was refluxed for 2 h. Removal of the solvent from the reaction mixture *in vacuo* and purification of the residue over a silica gel column and elution with a mixture of hexane and ethyl acetate (4:1) gave a mixture of *trans* and *cis* **3a, b** dienes in 90% yield, which could not be separated by usual column chromatography over silica gel and therefore the mixture of the diene (**3a, b**) was used as such for Diels–Alder reaction in which *cis*-diene (**3b**) was recovered unchanged. The base-catalyzed hydrolysis of **3b** followed by acidification yielded lactone (**13**).

2.2. *General procedure for Diels–Alder reaction*

A mixture of diene (**3a–b**) (1 mmol), dienophile **4–6** (2 mmol), hydroquinone (10 mg) and toluene (5 ml) was heated in a sealed tube at 160°C for 2–3 h (Table I). Removal of solvent over rotary evaporator followed by purification over a silica gel column and elution with a mixture of hexane and ethyl acetate (7:3) furnished adducts **8–11** as colourless liquids, except

when mentioned otherwise. Similarly, compound **12** was obtained from chalcone (**3c**) by reaction with methyl vinyl ether (**7**).

Compound **8**: IR (neat): ν_{max} 1725, 1680, 1610 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42 (1H, d, J = 1.9 Hz), 6.8 (4H, bs), 6.52 (1H, d, J = 10.1 Hz), 6.01 (1H, d, J = 10.1 Hz), 3.71 (3H, s), 3.18 (1H, dd, J = 1.9 and 10.3 Hz), 2.70 (1H, ddd, J = 10.3 and 13.2 Hz), 2.2 (3H, s), 2.10 (1H, dd, J = 5.9 and 11.5 Hz), 1.79 (1H, dt, J = 11.5 and 13.2 Hz), 1.4 (6H, s, $CH_3 \times 2$); Mass: (*m/z*) 324 (M^+); Anal. Calc. for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46%; Found: C, 77.69; H,7.51%.

Compound **9**: IR (neat): ν_{max} 2980, 1725, 1680, 1630, 1610, 1500, 1460, 1320, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 (1H, d, J = 1.9 Hz), 6.69 (1H, d, J = 10.3 Hz), 6.59 (2H, s, H-2', H-6'), 5.99 (1H, d, J = 10.3 Hz), 3.90 (6H, s, $OCH_3 \times 2$), 3.85 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.62 (1H, dd, J = 1.9 and 10.5 Hz), 2.90 (1H, dd, J = 5.9 and 11.5 Hz), 2.85 (1H, dd, 10.5 Hz), 2.11 (1H, dd, J = 5.9 and 13.5 Hz), 1.87 (1H, dt, J = 11.5 and 13.5 Hz), 1.2 (3H, s, CH_3), 1.1 (3 H, s, CH_3); Mass: (*m/z*) 400 (M^+); Anal. Calc. for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05%; Found: C, 68.91; H, 7.09%.

Compound **10**: IR ($CHCl_3$): ν_{max} 2970, 1775, 1690, 1615, 1460, 1245, 1170 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.5 (1H, s, H-3), 7.45 (1H, s, H-8), 5.32 (2H, s, H-9), 2.78 (2H, t, J = 6.85 Hz, H-5), 2.07 (2H, t, J = 6.85 Hz, H-6), 1.44 (6H, s); Mass: (*m/z*) 192 (M^+). Anal. Calc. for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13%; Found: C, 73.10; H, 6.06%.

Compound **11**: IR ($CHCl_3$): ν_{max} 2968, 2926, 1775, 1680, 1460, 1256, 1073 cm^{-1}; ^1H NMR (500 MHz $CDCl_3$): δ 8.5 (1H, s, H-3), 7.5 (1H, s, H-8), 6.9 (1H, d, J = 10 Hz, H-6), 6.45 (1H, d, J = 10 Hz, H-5), 5.34 (2H, s, H-9), 1.44 (6H, s, $CH_3 \times 2$); Mass: (*m/z*) 228 (M^+); Anal. Calc. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30%; Found: C,73.75; H, 5.25%.

Compound **12**: IR ($CHCl_3$): ν_{max} 2973, 1680, 1502, 1426 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.92 (1H, dd, J = 8.5 and 2.0 Hz), 7.80 (1H, dd, J = 2.0 Hz), 6.86 (1H, d, J = 8.5 Hz), 6.59 (1H, bs), 6.62 (1H, d, J = 10 Hz), 5.87 (1H, d, J = 10 Hz), 5.80 (1H, d, J = 2.0 Hz), 3.9 (2H, q, J = 7 Hz), 3.8 (3H, s), 2.88 (1H, dd, J = 2.0 and 5 Hz), 2.23 (3H, s), 2.03 (1H, m), 1.56 (2H, m), 1.30 (3H, s, CH_3), 1.29 (3H, s, CH_3), 1.29 (3H, t, J = 7 Hz, CH_2CH_3); Mass: (*m/z*) 368 (M^+).

Compound **13**: IR ($CHCl_3$): ν_{max} 2990, 1770, 1688, 1605, 1450, 1380, 1280, 1140, 1035 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.8 (1H, d, J = 10 Hz), 6.26 (1H, d, J = 10 Hz), 6.73 (2H, m), 5.42 (1H, d, J = 2.3 Hz), 3.19 (1H, dd, J = 2.3 and 7.3 Hz), 1.31 (6H, s, $CH_3 \times 2$); Mass: (*m/z*) 192 (M^+); Anal. Calc. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29%; Found: C, 68.89; H, 6.42%.

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