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Synthesis of optically active polycyclic compounds by Diels–Alder reactions of (+)-nopadiene

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Abstract—4-Oxo-2-cyclopentenylacetate **1** underwent a tandem Diels–Alder reaction with (+)-nopadiene **3** to lead to C_2-symmetric optically active polycyclic ketone **4**. All attempts to carry out similar processes with acetoxy ketone **1** and two different dienes, that is, (+)-nopadiene **3** and isoprene **6** or 2,3-dimethyl-1,3-butadiene **7** were unsuccessful. Enantiomerically pure polycyclic ketones **8** and **9** were prepared by Diels–Alder cycloaddition between optically active α,β-unsaturated ketone **5** and dienes **6** and **7**.

1. Introduction

4-Oxo-2-cyclopentenylacetate (4-acetoxy-2-cyclopenten-1-one) **1** has been shown to be a versatile compound that can be used in many reactions as a synthetic equivalent of cyclopentadienone **2** since it undergoes a rapid elimination reaction[1] (Fig. 1). Compound **2** is unstable, generally dimerizes and cannot be isolated or manipulated in the monomeric state. Ketone **1** has been used to prepare a variety of hydrofluorenones by a one-pot tandem Diels–Alder reaction.[2]

It was our aim to use ketone **1** and (+)-nopadiene **3** to develop a convenient synthesis of optically active polycyclic products. (+)-Nopadiene **3** is an inner–outer poorly reactive diene[3] easily available from chiral pool in both enantiomeric forms.

2. Results and discussion

When ketone **1** interacted with diene **3** (1:2.5 ratio of equivalents) under high pressure conditions[4] (9 kbar) and in the presence of a Lewis acid catalyst (Et_2AlCl) at 30 °C, only optically active polycyclic product **4** was obtained in 30% overall yield (Fig. 1). Attempts to carry out the reaction at atmospheric pressure always led to a

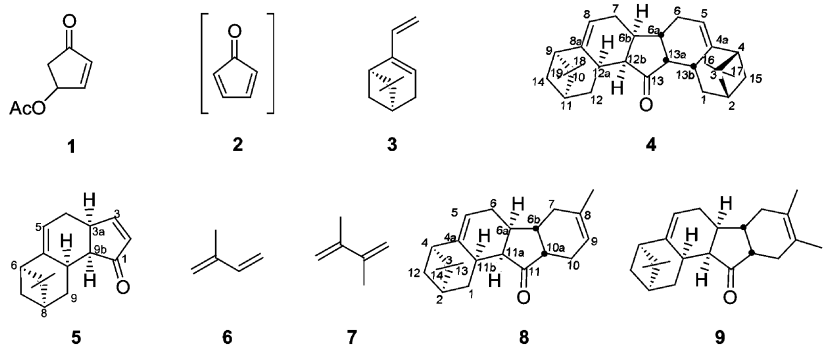

Figure 1.

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mixture of **4** and **5**; the best conditions led to a 1:1 mixture of **4/5** in low yield (18%).

The structure of C_2-symmetric ketone **4** was based on extensive NMR investigation. The regiochemistry of the carbonyl function was assigned by long-range hetero-correlation experiments. Selective pre-irradiation of H(12a) gave long-range hetero-correlations with C(6b), C(8), C(8a), C(12b) and C(13), while irradiation of H(8) gave long-range hetero-correlations with C(6b), C(9) and C(12a) (Fig. 2). The stereochemistry at the ring junctions, as well as the relationship of the dimethylcyclobutane ring with bridgehead hydrogens, were based on ^{1}H–{^{1}H}NOE experiments. Selective pre-irradiation of the resonance due to H(6a) resulted in signal enhancement of the resonances attributed to H(6), H(13a) and H(13b); enhancements also occurred on H(1), H(4) and H(13b) upon irradiation of the methyl group at 0.86 ppm (Fig. 2).

The overall configuration showed that polycyclic compound **4** was a 2:1 diene–enone adduct from a tandem Diels–Alder reaction.[5] The formation of **4** may be rationalized in view of the fact that acetoxy ketone **1** is a synthetic equivalent of cyclopentadienone **2**. Recently we showed[6] that when **1** and **3** (1:1.2 ratio of equivalents) interacted under high pressure or atmospheric pressure, only (+)-tetracyclic ketone **5** was obtained regioselectively and *anti*-(with reference to the *gem*-dimethylcyclobutane ring)-*endo* diastereoselectively. In the presence of an excess of diene **3**, the (+)-α,β-unsaturated ketone **5** reacted with a second molecule of diene, as previously observed in the cycloaddition reactions of **1** with open chain dienes,[5] leading to compound **4**. The second cycloaddition was also regioselective and *syn*-(with reference to the bridgehead H(3a)–H(9b) hydrogens)-*endo*-diastereoselective. The severe non-bonded interactions in the transition state from *anti*-addition favour strongly the diene *syn*-addition as clearly shown by the analysis of the Dreiding models.

Since tandem Diels–Alder reaction of acetoxy ketone **1** allows an easy preparation of polycyclic compounds, we tried to test the feasibility of this strategy to synthesize new optically active polycycles by using two different dienes in the multiple process, one was the enantiopure (+)-nopadiene **3** and the other was isoprene **6** or 2,3-dimethyl-1,3-butadiene **7**. In order to follow the reactions by GLC we first synthesized all of the expected products by a different route.

Both pentacyclic compounds **8** and **9** were prepared by $EtAlCl_2$-catalyzed cycloaddition reaction[4,7] between (+)-tetracyclic α,β-unsaturated ketone **5** and isoprene **6** or 2,3-dimethyl-1,3-butadiene **7** in 63% and 74% yield, respectively. The structures of **8** and **9** were assigned on the basis of the well-known outcome of the Diels–Alder reaction and on ^{1}H and ^{13}C NMR spectroscopy.

The analysis of the Dreiden models showed that the steric factors that favoured the *syn*-diastereoselectivity in the above discussed cycloaddition between **3** and **5**, favoured strongly also the *syn*-addition of dienes **6** and **7** in the cycloadditions with ketone **5**, thus justifying the structures assigned to **8** and **9**. Further support is given by ^{1}H and ^{13}C NMR data for compounds **8** and **9**. Decoupling, NOE and long-range experiments were performed in C_6D_6 solution, due to the overlap of the interesting protons of compounds **8** and **9** in $CDCl_3$ solution. The regiochemistry of the methyl group at C(8) of cycloadduct **8** is corroborated by the NOE enhancement observed on Hs(7) upon irradiation of 8-Me resonance at 1.54 ppm; furthermore selective irradiation of the 8-Me protons gave long-range hetero-correlation with C(7). The *cis*-stereochemical relationship between the dimethylcyclobutane ring and H(11b) for ketones **8** and **9** followed from the NOEs observed on the resonances of H(1) and H(11b) (Fig. 3) upon irradiation of methyl protons H(13) at 0.86 and 0.80 ppm for **8** and **9**, respectively. The $^3J_{11a,11b}$ (6.3 Hz for **8** and 6.7 Hz for **9**) and $^3J_{6a,11a}$ (8.5 and 8.6 Hz for **8** and **9**, respectively) con-

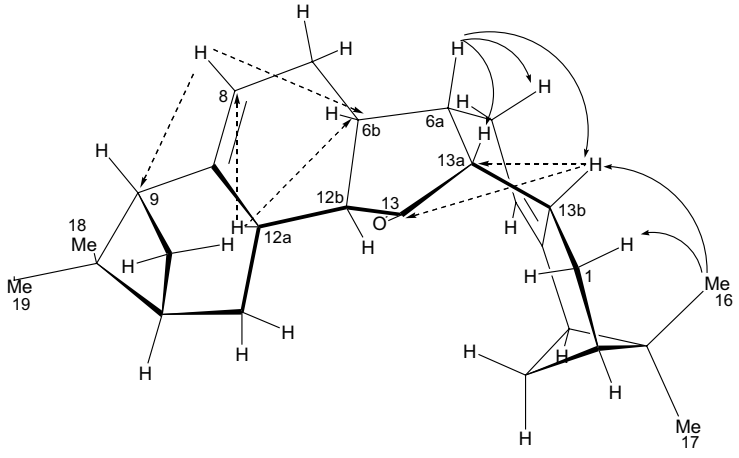

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Figure 2. Minimized energy conformation of compound **4**; the arrows indicate observed NOEs; dotted arrows indicate long-range hetero-correlations.

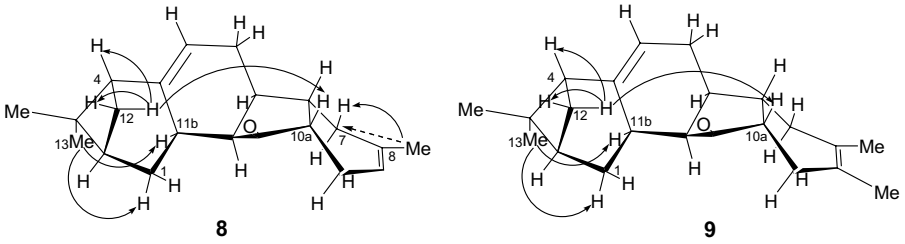

Figure 3. Minimized energy conformations of compounds **8** and **9**; the arrows indicate observed NOEs; dotted arrow indicates a long-range hetero-correlation.

firmed the *cis*-stereochemistry at the C(6a)–C(11a)–C(11b) ring junctions. Furthermore the configuration at C(6b)–C(10a) ring junction in both ketones **8** and **9** were confirmed by the NOEs observed on H(4) and H(10a) upon selective irradiation of H(12) (see Fig. 3).

The experiments of the multiple Diels–Alder reactions were carried out by adding (+)-nopadiene **3** (1 equiv) to the catalyst/ketone (1:1 ratio of equivalents) complex. After 3 h, diene **6** or **7** was added (1 equiv). The sequence of the addition of diene was based on their reactivity, the (+)-nopadiene **3** being less reactive than open-chain dienes **6** and **7** in the normal electron demand Diels–Alder reactions. Unfortunately very complex reaction mixtures were always obtained and, despite extensive efforts, we were not able to control these crossed tandem Diels–Alder reactions.

3. Conclusions

In conclusion a one-pot tandem Diels–Alder reaction between **1** and **3** allowed polycyclic ketone **4** to be synthesized in reasonable yield. Multiple attempts to carry out crossed tandem processes failed because they led to complex mixtures. Optically active polycyclic compounds **4**, **8** and **9** are interesting for synthetic applications in view of the facile conversion of the *gem*-dimethylcyclobutane ring into a variety of substituents.

4. Experimental[8]

4.1. Et_2AlCl-catalyzed Diels–Alder reaction of 4-oxo-2-cyclopentenyl-acetate 1 with (+)-nopadiene 3

A 1 M hexane Et_2AlCl solution (0.3 mL, 0.3 mmol) was added to a solution of 0.042 g (0.3 mmol) of 4-oxo-2-cyclopentenyl-acetate **1**[9] in 2 mL of dry CH_2Cl_2 and the mixture was stirred at 25 °C for 40 min.[10] A solution of (+)-nopadiene **3** (0.11 g, 0.74 mmol) in dry CH_2Cl_2 (1 mL) was then added, the whole mixture placed in a Teflon ampoule and CH_2Cl_2 added until the ampoule was completely filled. The ampoule was closed and kept under 9 kbar pressure for 7 h at 30 °C. After depressurizing, the mixture was poured into a cooled saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by column chromatography on silica gel eluting with 98:2 hexane–ethylacetate to afford ketone **4** (0.034 g, 30% yield) as a white crystalline product; mp 135–136 °C (methanol); $[\alpha]_D$ = +8.5 (*c* 0.448, $CHCl_3$); IR 1728 (s, C=O) cm^{-1}; ^1H NMR, δ 0.86 (s, 6H, Hs-16, Hs-18), 1.24 (s, 6H, Hs-17, Hs-19), 1.24 (ddd, 2H, J = 8.1, 3.3, 2.9 Hz, H-14, H-15), 1.89 (ddd, 2H, J = 17.3, 5.4, 4.4 Hz, H-6, H-7), 1.96 (m, 2H, H-2, H-11), 1.98 (m, 2H, H-1, H-12), 2.28 (ddd, 2H, J = 9.0, 8.1, 4.4 Hz, H-6a, H-6b), 2.34 (m, 4H, H-4, H-9, H-14, H-15), 2.39 (ddd, 2H, J = 17.3, 9.0, 3.0 Hz, H-6, H-7), 2.48 (ddd, 2H, J = 12.8, 7.2, 2.7 Hz, H-1, H-12), 2.51 (dd, 2H, J = 8.1, 5.8 Hz, H-12b, H-13a), 2.73 (ddd, 2H, J = 7.2, 5.8, 4.0 Hz, H-12a, H-13b), 5.26 (ddd, 2H, J = 5.4, 3.0, 2.9 Hz, H-5, H-8); ^{13}C NMR, δ 22.7 (C-16, C-18), 26.9 (C-17, C-19), 27.4 (C-1, C-12), 30.0 (C-6, C-7), 31.5 (C-14, C-15), 32.1 (C-12a, C-13b), 40.5 (C-3, C-10), 42.2 (C-2, C-6a, C-6b, C-11), 51.0 (C-4, C-9), 52.0 (C-12b, C-13a), 117.1 (C-5, C-8), 145.7 (C-4a, C-8a), 220.4 (C-13); MS, *m/z* (rel. int.) 376 (M^+, 22), 333 (47), 229 (58), 133 (79), 105 (base), 91 (97). Anal. Calcd for $C_{27}H_{36}O$: C, 86.12; H, 9.64. Found: C, 86.22; H, 9.61%.

A 1 M hexane solution of Et_2AlCl (0.3 mL, 0.3 mmol) was added to a solution of ketone **1** (0.042 g, 0.3 mmol) in dry toluene (2 mL) and the mixture was stirred at 25 °C for 40 min. A solution of (+)-nopadiene **3** (0.11 g, 0.74 mmol) in dry toluene (1 mL) was then added and the mixture heated at 30 °C for 72 h. Usual work up gave a residue (0.016 g, 18%), which was shown to be a 1:1 mixture of **4** and **5** by GLC analysis.

4.2. Diels–Alder reaction of (+)-ketone 5 with isoprene 6

A 1 M hexane solution of $EtAlCl_2$ (0.4 mL, 0.4 mmol) was added to a solution of (+)-ketone **5** (0.19 g, 0.8 mmol) in dry CH_2Cl_2 (5 mL) and the mixture was stirred at 25 °C for 40 min. Isoprene (**6**) (0.5 mL, 4.8 mmol) was then added and the mixture was heated at reflux temperature for 27 h. The reaction mixture was poured into a cooled saturated aqueous $NaHCO_3$ solution, extracted with CH_2Cl_2, dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2) eluting with 98:2 hexane–ethylacetate to afford compound **8** (0.15 g, 63% yield); mp 93–94 °C (ethylacetate); $[\alpha]_D$ = +34 (*c* 0.396, $CHCl_3$); IR 1725 (s, C=O) cm^{-1}; ^1H NMR, δ 0.86 (s, 3H, Hs-13), 0.82 (d, 1H, J = 9.2 Hz, H-12), 1.23 (s, 3H, Hs-14), 1.52 (m, 1H, H-7), 1.54 (s, 3H, 8-Me), 1.98 (ddd, 1H, J = 6.7,

5.5, 2.8 Hz, H-2), 2.00 (m, 1H, H-10), 2.05 (m, 1H, H-7), 2.06 (m, 1H, H-6), 2.08 (m, 2H, H-1, H-6b), 2.23 (m, 1H, H-10a), 2.28 (m, 1H, H-12), 2.31 (d, 1H, $J = 5.5$ Hz, H-4), 2.39 (d, 1H, $J = 8.5$ Hz, H-6a), 2.40 (m, 1H, H-6), 2.43 (m, 1H, H-10), 2.55 (dd, 1H, $J = 8.5$, 6.3 Hz, H-11a), 2.60 (ddd, 1H, $J = 13.7$, 5.1, 2.8 Hz, H-1), 2.68 (ddd, 1H, $J = 7.1$, 6.3, 2.8 Hz, H-11b), 5.27 (s, 1H, H-9), 5.46 (dd, 1H, $J = 6.5$, 3.3 Hz, H-5); ^{13}C NMR, δ 21.7 (C-10), 22.4 (C-13), 24.1 (8-Me), 26.4 (C-14), 26.7 (C-1), 29.3 (C-6), 30.1 (C-12), 33.5 (C-11b), 33.7 (C-7), 39.7 (C-6a), 40.9 (C-3), 41.1 (C-6b), 41.9 (C-2), 48.7 (C-11a), 48.9 (C-10a), 50.1 (C-4), 118.5 (C-5), 119.4 (C-9), 131.9 (C-8), 146.9 (C-4a), 220.2 (C-11); MS, *m*/*z* (rel. int.) 296 (M^+, 15), 278 (14), 253 (22), 149 (100), 148 (30), 131 (32), 105 (55), 91 (97), 79 (27). Anal. Calcd for $C_{21}H_{28}O$: C, 85.08; H, 9.52. Found: C, 85.19; H, 9.50%.

4.3. Diels–Alder reaction of (+)-ketone 5 with 2,3-dimethyl-1,3-butadiene 7

(+)-Ketone **5** (0.228 g, 1 mmol) in CH_2Cl_2 (6 mL), $EtAlCl_2$ (0.5 mL, 1 M hexane solution), 2,3-dimethyl-1,3-butadiene **7** (0.35 mL, 6 mmol) in CH_2Cl_2 (4 mL) interacted according to the above-described procedure for 15 h at reflux temperature. The reaction mixture was worked up as usual and ketone **9** (74% yield) was purified by column chromatography (SiO_2) eluting with 98:2 hexane–ethylacetate; mp 91–92 °C (ethylacetate); $[\alpha]_D = +24$ (*c* 0.478, $CHCl_3$); IR 1725 (s, C=O) cm^{-1}; ^{1}H NMR, δ 0.80 (s, 3H, Hs-13), 0.82 (d, 1H, $J = 9.0$ Hz, H-12), 1.23 (s, 3H, Hs-14), 1.51 (m, 1H, H-7), 1.54 (s, 3H, 8-Me), 1.58 (s, 3H, 9-Me), 1.98 (ddd, 1H, $J = 6.8$, 5.5, 2.8 Hz, H-2), 2.00 (m, 1H, H-10), 2.02 (m, 1H, H-7), 2.03 (m, 1H, H-6b), 2.04 (m, 1H, H-6), 2.05 (m, 1H, H-1), 2.25 (m, 1H, H-12), 2.26 (ddd, 1H, $J = 7.2$, 6.0, 1.3 Hz, H-10a), 2.29 (d, 1H, $J = 5.6$ Hz, H-4), 2.32 (m, 1H, H-10), 2.37 (d, 1H, $J = 8.6$ Hz, H-6a), 2.38 (m, 1H, H-6), 2.54 (dd, 1H, $J = 8.6$, 6.7 Hz, H-11a), 2.59 (ddd, 1H, $J = 13.6$, 5.1, 2.8 Hz, H-1), 2.66 (ddd, 1H, $J = 7.1$, 6.7, 2.8 Hz, H-11b), 5.45 (ddd, 1H, $J = 6.8$, 3.0, 2.7 Hz, H-5); ^{13}C NMR, δ 18.9, 19.5 (8-Me, 9-Me), 22.3 (C-13), 24.8 (C-10), 26.4 (C-14), 26.7 (C-1), 29.3 (C-6), 30.1 (C-12), 33.4 (C-11b), 35.7 (C-7), 39.6 (C-6a), 40.9 (C-3), 41.3 (C-6b), 41.9 (C-2), 48.9 (C-11a), 50.0 (C-10a), 50.1 (C-4), 118.5 (C-5), 123.8 (C-8), 124.1 (C-9), 146.9 (C-4a), 220.5 (C-11); MS, *m*/*z* (rel. int.) 310 (M^+, 24), 292 (15), 267 (20), 249 (15), 163 (100), 145 (29), 133 (30), 119 (39), 105 (51), 91 (63). Anal. Calcd for $C_{22}H_{30}O$: C, 85.11; H, 9.74. Found: C, 85.20; H, 9.69%.

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