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Synthesis of 2,2-Disubstituted Pentalenes and Indenes by a Useful Modification to Nakamura's DMCP [3+2]-Cycloaddition Protocol

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Abstract

A two-pot tactic is presented to reach the oxidized 2,2-dimethyl-substituted pentalene and indene ring systems.

Keywords

illudin; trimethylenemethane; [3+2]-cycloaddition; 5, 6-fused-ring systems; indene; pentalene; ketene acetal methylation

The illudin family of natural products is a large group of sesquiterpenes of which many members display antibacterial and antitumor properties. It appears to us that the constituents in the family may be biosynthetically derived by postmetabolic selective oxidations of allylic and primary functionality in illudin D (**1**) followed by the necessary eliminations of hydroxy residues and/or epimerization of the α -methyl ketone functionality (Figure 1). However, *de novo* conventional diastereoselective synthetic strategies applicable to the oxidized *gem*-dimethyl residue found in compounds **3–9** are not easily imagined. The structure that is most often identified with the family is the diene illudin M (**2**) and all but one,^{1c} of the past syntheses and strategies were aimed at this compound or its derivatives where the *gem*-dimethyl functionality remains unoxidized.¹

Motivated by some recent reports of unusual divergent antibiotic activity against methicillin-resistant *Staphylococcus aureus* (MRSA),² we became interested in pursuing a new strategy for construction of the oxidized illudins **4–9**, along with illudinic acid (**3**). To this end, we chose to examine a slightly modified [3+2]-cycloaddition procedure developed by Nakamura that employed 6,6-dimethyl-1-methylene-4,8-dioxaspiro[2.5]octane (**10**) as a masked and stabilized dipolarophile (Scheme 1).³ This species, which displays both dipolar and biradical characteristics, participates in both concerted and stepwise reactions.⁴ While the nature of this intermediate and its preferred manifold of reactivity are debatable,⁵ compound **10** offers quick access to complex adducts derived from an assortment of unsaturated esters and enones. Surprisingly, however, 1,1-dialkoxy-2-methylenecyclopropanes (DMCP) have rarely been utilized with unsaturated systems displaying α - and β -substitution, which could be imagined as useful in natural product synthesis, particularly for some of the oxidized members of the illudin family.

We therefore elected to examine the combination of DMCP **10** with a wide scope of five-, six-, and seven-membered cycloalkenones including enones displaying α - and β -substitution on the unsaturated portion so that we might better understand its predilections (Table 1). Our plan was to cause the elimination of the substituent and thereby afford the desired pentalene, indene or azulene system. If the reaction proved successful, we further conjectured that it could be applied with the appropriated α - or β -substituted cyclohexenone to reach some of the oxidized members of the illudins.

First, we examined the combination of DMCP **10** with both cyclohexenone (**11a**) and cyclopentenone (**11f**; Table 1, entries 1 and 8). The resulting adducts were quite sensitive to moisture. So, for the ensuing study we found it very convenient to carry out the reactions in a deuterated solvent within a sealed NMR tube so that we could compare the integration of ^1H NMR signals of the product against a known standard for an estimation of the percent yield. Both of these combinations, which lead to adducts **12a** and **12f**, had been previously examined by Nakamura; the latter was even the focus of a procedure in Organic Synthesis.³ We were therefore gratified to find that our yields for adducts **12a** and **12f** were within 5% of those previously reported.^{3,5f}

Next, we screened an assortment of α - and β -substituted cyclic enone **11j–q** that we imagined might undergo subsequent elimination. However, no product was observed over a range of conditions; warming with the DMCP **10** with the respective cyclic enones **11j–q** simply returned partially degraded starting materials.

On the other hand, the five- and six-membered cycloalkenones **11b–e** and **11g–h** underwent reaction with the DMCP **10** to afford the respective ketene acetal intermediates **12b–e** and **12g–h**, respectively. The yields of the α -substituted cycloalkenones ranged from 42–61%. The only β -substituted system to undergo a [3+2]-cycloaddition amongst those examined was the β -selenide **11b**. However, the yield from its union with **10** was significantly lower than the successful examples of the corresponding α -substituted cyclohexenones. In addition to the ketene acetal **12**, the exocyclic methylene adduct **13** was also observed. The relative ratio of this side product, however, was not affected by our choice of solvent used in the reaction. Nakamura had previously reported that very electron-deficient systems such as nitroalkenes often preferred the reaction manifold leading to product **13**, and he attributed it to the intervention of a single-electron-transfer cycloaddition pathway.^{5d} We also observed adducts corresponding to the known class of *ortho*-ester **14** present in appreciable quantities (5% yield) for nearly all of the cycloalkenone reactions (**11c–d** and **11g–h**). The appreciable quantity of **14** across the series may reflect undesirable steric effects for cyclic enone displaying α -substituents. We also observed that cycloheptenone (**11i**) provided the ketene acetal **12i**, for the first time, albeit in much lower yield than the corresponding unsubstituted five- or six-membered cyclic enones that afforded **12f** and **12a** respectively. However, our success for seven-membered enones was limited to this particular example, as neither the α -substituted cycloheptenone **11p** nor **11q** participated in the [3+2]-cycloaddition.

Next, we decided to tackle the problem of ketene acetal stability. Protonation of the similar 5,5- and 5,6-fused ketene acetals reportedly affords a 1:1 thermodynamic ratio of the corresponding diastereomeric esters. Thus, this issue needed to be addressed before prompting elimination of the α -substituent. Initially, the crude ketene acetal was subjected to a modified Simmons–Smith reaction.⁶ Analysis of the crude ^1H NMR suggested a modest yield of the corresponding cyclopropane. However, before we could further optimize these conditions, we discovered a much simpler methylation method. Introduction of methyl iodide upon conclusion of the cycloaddition, as determined by TLC or ^1H NMR, and resumption of heating (24 h) afforded the respective homologated products **15a–i**, which could be isolated and further purified by chromatography (Table 2). We found that the

ketene acetal undergoes kinetic methylation in good yield with 2:1 diastereoselectivity in all cases (30–67% yield from the respective **11**). We speculate that the X (Cl, Br, SePh) and methyl (Me) residues are positioned on the convex, β -face of the fused ring system.

To complete the model for the corresponding oxidized 2,2-dimethyl-substituted pentalene and indene ring systems, we examined modes of elimination for the bromide and the phenyl selenide substituents (Scheme 2). Both base-induced α -elimination of the bromide, and oxidation-induced *syn* elimination of the α -phenyl selenide, afforded the enone functionality found in the pentalene **16** and the indene **17** (70–75% yield from diastereomeric mixture, 30–40% yield from the respective cyclic enone **11**). Further reduction of the carbonyl functionality in **16** and **17** (in toluene, 6 equiv DIBAL-H in hexanes), followed by MnO₂ oxidation of the crude allylic alcohol yielded **18** and **19** (83–85% yield) and completed the model.

In conclusion, it appears that the Nakamura procedure is not effective for the construction of α -substituted [5.3.0]-bicycles that might be elaborated into the corresponding azulenes. However, we have found a straightforward tactic for the construction of complex 2,2-dimethyl-substituted pentalene and indene ring systems.⁷ The process involves the sequential [3+2]-cycloaddition reaction of DMCP **10** with an α -bromide or α -phenyl selenide in a five- or six-membered cycloalkenone, followed by methylation and cleavage of the intermediate ketene acetal with methyl iodide, and elimination of the appropriated α -substituent. The sequence can be carried out without chromatography and results in 30–40% yield. Further bisreduction and monooxidation of the allylic alcohol provides access to oxidized 2,2-dimethyl-substituted pentalene and indene ring systems. We postulate that such a sequence may be well suited for construction of the 2,2-disubstituted hydrindane skeletons found in the illudins **3–9** from the chiral cyclohexadienone **20** (Scheme 3).

Acknowledgments

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7. **Preparation of 15; Representative Procedure for Ester 15c:** Compounds **11c** (0.123 g, 0.489 mmol) and **10** (0.038 g, 0.246 mmol) were dissolved in CD₃CN (0.500 mL) and heated in a sealed NMR tube at 80 °C for 0.5 h. Additional **10** (0.100 g, 0.648 mmol) was added to the reaction mixture and it was heated for 2 h. After cooling to r.t., MeI (0.150 mL, 2.41 mmol) was added and the reaction mixture was heated to 80 °C for 24 h. Afterwards, the mixture was concentrated in vacuo and purified by silica gel chromatography (75% CH₂Cl₂–hexanes) to afford **15c** as a light yellow oil (0.074 g, 41% based on recovered starting material); *R_f* = 0.22 (75% CH₂Cl₂–hexanes). ¹H NMR (500 MHz, CDCl₃): δ = 7.47 (d, *J* = 7.1 Hz, 2 H), 7.36 (d, *J* = 6.8 Hz, 1 H), 7.30 (t, *J* = 7.9 Hz, 2 H), 3.84 (q, *J* = 10.5 Hz, 2 H), 3.12–3.17 (m, 3 H), 2.75 (m, 1 H), 2.13–2.28 (m, 3 H), 1.99 (m, 2 H), 1.86 (d, *J* = 14.4 Hz, 1 H), 1.64 (m, 3 H), 1.37 (s, 3 H), 1.05 (s, 6 H). ¹³C NMR (125 MHz, CDCl₃): δ = 205.7, 177.2, 136.8, 129.5, 129.3, 129.1, 71.3, 47.2, 47.1, 46.4, 40.7, 37.3, 34.7, 27.1, 24.8, 24.5, 24.4, 22.2, 19.3. IR (thin film): 3505, 2959, 2932, 2870, 1728, 1693, 1462, 1207, 1134, 741 cm⁻¹. HRMS: *m/z* calcd for C₂₂H₂₉IO₃Se: 548.0327; found: 548.0340. Selected data of *ortho*-ester **14d**: *R_f* = 0.20 (5% EtOAc–hexanes). ¹H NMR (500 MHz, CDCl₃): δ = 6.30 (t, *J* = 4.1 Hz, 1 H), 5.48 (t, *J* = 2.4 Hz, 1 H), 5.17 (t, *J* = 2.4 Hz, 1 H), 4.09 (d, *J* = 10.3 Hz, 1 H), 4.01 (d, *J* = 10.3 Hz, 1 H), 3.42 (m, 2 H), 3.14 (dt, *J* = 16.1, 2.7 Hz, 1 H), 2.53 (dt, *J* = 16.1, 1.9 Hz, 1 H), 2.15 (m, 1 H), 2.06 (m, 2 H), 1.90 (m, 1 H), 1.81 (m, 1 H), 1.63 (m, 1 H), 1.26 (s, 3 H), 0.78 (s, 3 H). Selected data for exocyclic methylene adduct **13e**: *R_f* = 0.28 (10% EtOAc–hexanes). ¹H NMR (500 MHz, CDCl₃): δ = 5.50 (t, *J* = 2.4 Hz, 1 H), 5.25 (t, *J* = 2.1 Hz, 1 H), 3.66 (m, 1 H), 3.59 (m, 2 H), 3.40 (d, *J* = 11.3 Hz, 1 H), 2.87 (m, 2 H), 2.68 (m, 3 H), 2.27 (dd, *J* = 16.8, 2.7 Hz, 1 H), 1.98 (m, 1 H), 1.87 (m, 1 H), 1.75 (m, 1 H), 0.94 (s, 3 H), 0.93 (s, 3 H). **Preparation of 16 and 17; Representative Procedure from Bromide:** Compound **12d** (0.010 g, 0.021 mmol) was dissolved in THF (1.0 mL) and cooled to 0 °C. To the solution was added DBN (0.020 mL, 0.162 mmol) and the reaction was stirred at 0 °C to r.t. for 14 h. The reaction mixture was filtered through a pad of silica gel then concentrated in vacuo. The crude residue was purified by silica gel chromatography (15% EtOAc–hexanes) to afford **16** as a colorless oil (0.0060 g, 72% yield, 40% overall yield from **11d**). Data for compound **16**: *R_f* = 0.10 (20% EtOAc–hexanes). ¹H NMR (500 MHz, CDCl₃): δ = 3.95 (s, 2 H), 3.21 (d, *J* = 16.4 Hz, 1 H), 3.18 (s, 2 H), 2.93 (d, *J* = 16.2 Hz, 1 H), 2.74 (s, 2 H), 2.55 (s, 2 H), 2.45 (d, *J* = 18.8 Hz, 1 H), 2.36 (d, *J* = 16.1 Hz, 1 H), 1.44 (s, 3 H), 1.09 (s, 6 H). ¹³C NMR (125 MHz, CDCl₃): δ = 203.7, 183.4, 176.6, 146.1, 71.6, 54.2, 43.9, 40.8, 37.2, 34.7, 26.7, 26.0, 24.3, 18.6. IR (thin film): 2962, 2928, 1732, 1697, 1643, 1377, 1215, 1169, 1111 cm⁻¹. HRMS: *m/z* calcd for C₁₅H₂₁IO₃Na: 399.0433; found: 399.0430. **Procedure from Phenyl Selenide:** Compound **15c** (0.027 g, 0.049 mmol) was dissolved in CH₂Cl₂ (1.0 mL). To the solution was added H₂O (0.020 mL) followed by H₂O₂ (30% w/w in H₂O, 0.13 mL, 0.104 mmol). The reaction was then stirred for 1.5 h. The reaction was quenched with sat. aq NaHCO₃ and diluted with CH₂Cl₂. The aqueous layer was extracted with CH₂Cl₂ (3 ×) and the combined organics were washed with brine, dried (Na₂SO₄), and concentrated in vacuo. The crude residue was purified by silica gel chromatography (15% EtOAc–hexanes) to afford **17** as a colorless oil (0.014 g, 74% yield). Data for compound **17**: *R_f* = 0.14 (15% EtOAc–hexanes). ¹H NMR (500 MHz, CDCl₃): δ = 3.93 (s, 2 H), 3.23 (dt, *J* = 2.3, 14.0 Hz, 1 H), 3.18 (s, 1 H), 3.04 (dt, *J* = 2.3, 14.0 Hz, 1 H), 2.54 (d, *J* = 13.9 Hz, 1 H), 2.45 (d, *J* = 14.0 Hz, 1 H), 2.41 (m, 2 H), 2.34 (m, 2 H), 2.06 (quint, *J* = 6.5 Hz, 2 H), 1.39 (s, 3 H), 1.09 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 197.6, 177.0, 162.6, 135.5, 71.4, 48.9, 47.1, 41.4, 37.7, 34.7, 26.6, 26.2, 24.3, 23.5, 18.7. IR (thin film): 2962, 2978, 2870, 1732, 1666, 1393, 1184 cm⁻¹. HRMS: *m/z* calcd for C₁₆H₂₃IO₃Na: 413.0590; found: 413.0595. **Preparation of 18 and 19; Representative Procedure from Ester 17:** To a cooled (–78 °C) solution of **17** (0.016 g, 0.041 mmol) in toluene (0.5 mL) was added DIBAL-H (1 M in hexanes, 0.246 mL, 0.246 mmol). The resulting solution was stirred at –78 °C for 1 h. The reaction was quenched with 1 M aq Rochelle's salt, diluted with EtOAc, and stirred vigorously for 1 h. The aqueous layer was extracted with EtOAc (4 ×). The combined organics were washed with brine, dried with Na₂SO₄ and concentrated in vacuo to afford an inconsequential mixture (ca. 1:1) of allylic alcohols. The crude product was sufficiently pure for the subsequent reaction. However, the mixture of allylic alcohols could be separated by silica gel chromatography (40% EtOAc–hexanes → 75% EtOAc–hexanes) with *R_f* = 0.55 and 0.48 (75% EtOAc–hexanes) (combined mass of 0.0060 g, 86% yield). The crude mixture of allylic alcohols (0.0060 g, 0.033 mmol) was dissolved in CH₂Cl₂ (1.0 mL). MnO₂ (0.069 g, 0.78 mmol) was added to the flask and the reaction was stirred at r.t. for 12 h. The mixture was filtered through Celite and concentrated in vacuo. The crude residue

was purified by silica gel chromatography (40% EtOAc–hexanes → 50% EtOAc–hexanes) to afford **19** as a colorless oil (0.0049 g, 83% yield). Data for compound **19**: R_f = 0.15 (40% EtOAc–hexanes). ^1H NMR (500 MHz, CDCl_3): δ = 3.46 (s, 2 H), 2.67 (d, J = 18.4 Hz, 1 H), 2.49 (d, J = 15.6 Hz, 1 H), 2.38 (m, 2 H), 2.22–2.35 (m, 4 H), 2.04 (quint, J = 6.6 Hz, 2 H), 1.13 (s, 3 H). ^{13}C NMR (125 MHz, CDCl_3): δ = 164.1, 136.3, 70.8, 47.7, 42.4, 39.5, 37.7, 26.9, 25.1, 23.6 (C=O carbon unresolved). IR (thin film): 3413, 2924, 2854, 1651, 1393, 1045 cm^{-1} . HRMS: m/z calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$: 180.1150; found: 180.1148.

Figure 1.

Illudin D and illudin M, as well as some of the more synthetically challenging members of the illudin family, which may be accessed in biosynthetic fashion from oxidation of illudin D.

Scheme 1.

The degenerate dipolarophiles (a) and (a') form upon rupture of the cyclopropane ring. After a slight twist and flattening of the six-membered ring, these (a and a') would also become degenerate with (b).

Scheme 2. Reagents and conditions

(a) for X = Br, DBN, THF, 72–74% yield; (b) for X = SePh, H₂O₂, CH₂Cl₂–H₂O (10:1), 70–76% yield; (c) DIBAL-H, toluene, –78 °C, 77–86% yield; (d) MnO₂, CH₂Cl₂, 83–85% yield.

Scheme 3.

A postulated strategy for synthesizing some of the oxidized illudins from cyclohexadienone **20** using this new tactic

Table 1

[3+2]-Cycloaddition of DMCP with a Variety of Cyclic Enones^a

Entry	Cycloalkenone	Solvent ^b	Temp (°C)	Time (h)	Yield ^c (%) of 12	Yield ^c (%) of 13	Yield ^c (%) of 14	Major product
1		MeCN	80	24	69	<3	<3
2		DMF	80	24	20	<3	<3
3		MeCN	80	2.5	48	10	5
4		DMF	80	2.5	42	10	5
5		MeCN	80	2.5	61	12	5
6		CH ₂ Cl ₂	120	6	52	12	6 ^d

Entry	Cycloalkenone	Solvent ^d	Temp (°C)	Time (h)	Yield ^c (%) of 12			Yield ^c (%) of 13	Yield ^c (%) of 14	Major product
7		MeCN	80	2.5	52			10 ^d	5
8		MeCN	60	12	74			<3	<3
9		MeCN	60	18	50			7	5
10		MeCN	60	18	44			9	6

Entry	Cycloalkenone	Solvent ^b	Temp (°C)	Time (h)	Yield ^c (%) of 12	Yield ^c (%) of 13	Yield ^c (%) of 14	Major product
11								
12		MeCN	100	36	38	<3	<3	
13								
14								

^a Compounds **11j-q** proved unproductive in combination with the DMCP **10**.

^b Deuterated solvent.

^c Yield based on NMR comparison to a standard unless otherwise noted.

^d Isolated yield after chromatography.

Table 2

Methylation and Cleavage of Ketene Acetals by MeI

Entry	Reactant	Method ^a	Yield ^b (%)	Product ^c
1	12a	II	92 (63)	<p>15a</p>
2	12c	I	89 (42)	<p>15c</p>
3		II	91 (38)	
4	12d	I	91 (56)	<p>15d</p>
5		III	91 (47)	
6	12e	II	92 (48)	<p>15e</p>
7	12g	II	90 (45)	<p>15g</p>
8	12h	I	85 (37)	<p>15h</p>

Entry	Reactant	Method ^a	Yield ^b (%)	Product ^c
9	12i	II	80 (30)	<p style="text-align: center;">15i</p>

^a Method I: DMF-*d*₇, 80 °C; Method II: CD₃CN, 80 °C; Method III: CD₂Cl₂, 120 °C.

^b Yields based on NMR comparison to a known standard. Yields in parentheses are the overall yields from **11**.

^c R = the chain CH₂CMe₂CH₂I.