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Tetrahedron Letters 44 (2003) 1259–1261

TETRAHEDRON LETTERS

An efficient constructive method for a tricyclic system: an important intermediate for the synthesis of tricycloclavulone

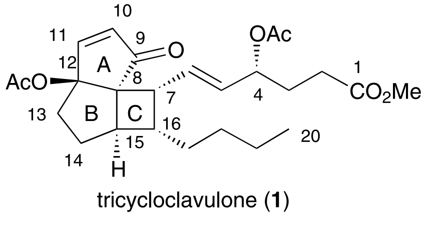
Hisanaka Ito,* Tatsuya Kobayashi, Mineki Hasegawa and Kazuo Iguchi*

School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 17 October 2002; revised 6 December 2002; accepted 6 December 2002

Abstract—The tricyclic ring system of tricycloclavulone was synthesized from 2-methoxycarbonyl-2-cyclopenten-1-one (**2**). Key reactions include Lewis acid-catalyzed [2+2]-cycloaddition of α,β-unsaturated ester **2** with thioacetylene derivatives and construction of the A-ring by using the Grubbs catalyst. © 2003 Elsevier Science Ltd. All rights reserved.

Tricycloclavulone (**1**) is an unusual prostanoid-related compound recently found by our group from the marine soft coral, *Clavularia viridis*[1] (Fig. 1). The relative stereochemistry of the chiral centers on the tricyclic core of **1** was established by the analysis of spectroscopic data. The relative stereochemistry of the acetoxyl-bearing carbon at C-4 on the α-chain as well as the absolute stereochemistry of **1** were speculatively based on consideration of the biosynthesis of **1**. The biological activity of compound **1** has not been examined yet owing to the small amount available. This structurally intriguing molecule consists of a highly functionalized and strictly fixed 5,5,4-tricyclic ring system having five chiral centers. The diverse structural feature of tricycloclavulone in conjunction with it's potential for biological activity has stimulated considerable interest. We report herein a stereocontrolled synthesis of the tricyclic core **3** of tricycloclavulone (**1**).



tricycloclavulone (**1**)

Figure 1.

Our synthetic strategy for tricycloclavulone (**1**) is outlined in Scheme 1. For the preparation of the side-chain modified analogues, we envisioned constructing the tricyclic ring system, having some functional groups to introduce side chains, at the early stage. The functionalized tricyclic intermediate **3** would be prepared by ring-closing olefin metathesis of divinyl compound **4** using a Grubbs catalyst. The compound **4** would be prepared by Lewis acid-catalyzed [2+2]-cycloaddition reaction of **2** with phenylthioacetylene and following vinylation of both carbonyl moieties on **5**. For the introduction of side chains, a vinyl sulfone moiety must be employed on the C-ring. The stereoselective introduction of both side chains would be achieved by the 1,4-addition of organometallics to the vinyl sulfone moiety and following capture of the resulting anion on the sulfone-bearing carbon by appropriate carbon electrophiles which can be converted to α-chain. This one-pot reaction should proceed at the convex face of the C ring.

Compound **4**, a precursor of the ring-closing metathesis for the construction of the tricyclic ring system, was synthesized as shown in Schemes 2 and 3. Although intramolecular [2+2]-cycloaddition reaction of the 2-alkoxycarbonyl-2-cyclopenten-1-one derivatives has been reported,[2] to our best knowledge, there is no example for the Lewis acid-catalyzed intermolecular [2+2]-cycloaddition reaction of compound **2**. Therefore, we examined the conditions of Lewis acid-catalyzed [2+2] reaction of the easily available compound **2**[3] with phenylthioacetylene.[4] Under titanium(IV) chloride mediated conditions, 1,4-addition product **6** was produced and the desired **5** was not obtained (Scheme 2).

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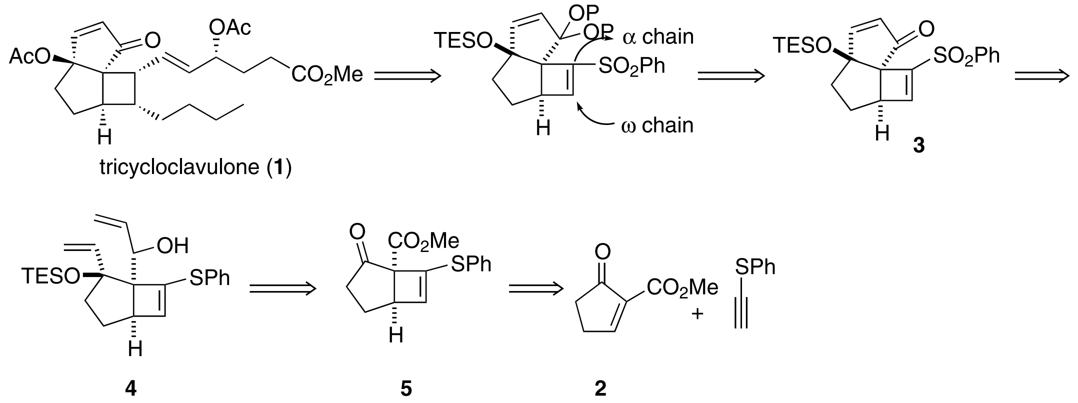
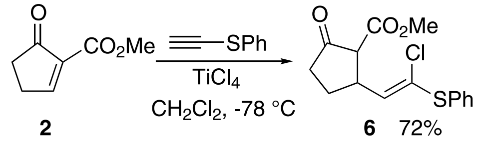
* Corresponding authors. Tel.: +81-426-76-5473; fax: +81-426-76-7282 (H.I.); Tel.: +81-426-76-7273; fax: +81-426-76-7282 (K.I.); e-mail: itohisa@ls.toyaku.ac.jp; onocerin@ls.toyaku.ac.jp

PII: S0040-4039(02)02814-9

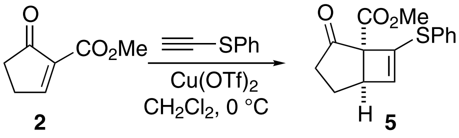


Scheme 1.



Scheme 2.

Table 1.

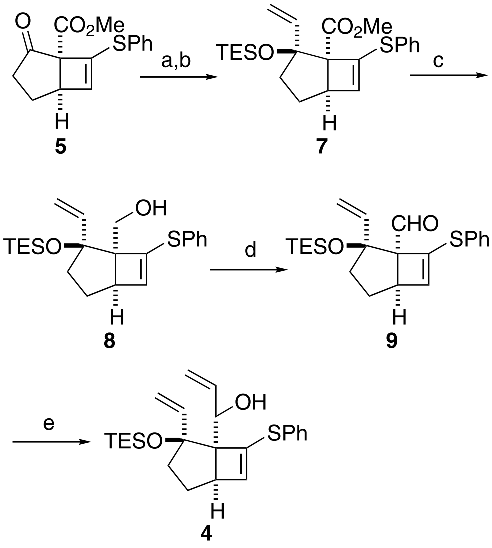


Entry	$Cu(OTf)_2$ (mol%)	Time	Yield (%)
1	100	10 min	70
2	30	3 h	64
3	20	5 h	52

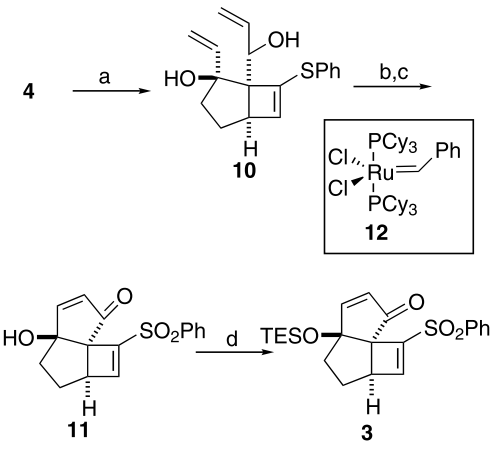
To prevent the reaction of the chloride anion to the carbocation intermediate, we employed copper(II) trifluoromethanesulfonate ($Cu(OTf)_2$) as a Lewis acid (Table 1). The reaction proceeded smoothly to give the desired bicyclic compound **5**[5] in the presence of an equimolar amount of $Cu(OTf)_2$ (entry 1). The reaction catalyzed by the Lewis acid was optimized and a better result was obtained in the use of 30 mol% of $Cu(OTf)_2$ (entry 2).

One-pot introduction of vinyl groups to both ketone and ester moieties on compound **5** was then examined (Scheme 3). Vinylation to the ketone moiety of **5** from the convex face by using small excess of vinylmagnesium bromide proceeded to give **7** as a single diastereomer with quantitative yield. On the other hand, the employment of a large excess of vinylmagnesium bromide (5 equiv.) to introduce a vinyl group to the ester moiety of **5** could not be achieved even at high temperature (40°C) and compound **7** was obtained. Therefore, the ester moiety was converted to an aldehyde to introduce the second vinyl group. After protection of the tertiary alcohol by a TES group, the resulting compound **7** was converted to aldehyde **9** in excellent yield. Vinylation of **9** by using vinylmagnesium bromide was achieved to give **4** as a diastereomeric mixture (1:1) in a moderate yield (60%) along with compound **8** (30%).[6] The yield of **4** was significantly improved (91%, dr = 1.5:1) by using vinyllithium[7] as a nucleophile without the production of **8**.

The effort for the construction of the tricyclic intermediate **3** is shown in Scheme 4. Ring-closing metathesis of compound **4** did not proceed in the presence of Grubbs catalyst **12**[8] in toluene at 100°C, because of the steric repulsion of the triethylsilyl group. Compound **4** was thus converted to **10** and the ring-closing metathesis of compound **10** was examined again. The ring-closing reaction of **10** in the presence of Grubbs catalyst **12** smoothly proceeded to give a tricyclic compound in excellent yield as a diastereomeric mixture. The synthesis of the important tricyclic vinyl sulfone intermediate **3**[9] was achieved by the oxidation of both hydroxyl and thioether groups using an excess of Dess–Martin periodinane in wet dichloromethane[10] followed by protection of the hydroxyl group by a TES group.



Scheme 3. *Reagents and conditions*: (a) vinylMgBr, THF, 0°C (100%); (b) TESOTf, lutidine, CH_2Cl_2, 0°C (97%); (c) $LiAlH_4$, Et_2O, 0°C (100%); (d) Dess–Martin periodinane, CH_2Cl_2, rt (95%); (e) vinyllithium, THF, −78°C (91%).



Scheme 4. *Reagents and conditions*: (a) TBAF, THF, rt (93%); (b) Grubbs catalyst **12**, toluene, 50°C (92%); (c) Dess–Martin periodinane, CH_2Cl_2, rt (89%); (d) TESOTf, lutidine, CH_2Cl_2, 0°C (100%).

In conclusion, a highly efficient synthetic method for the 5,5,4-tricyclic ring system of unusual prostanoid-related tricycloclavulone was developed. Construction of a tricyclic system as an enantiomerically pure form and the total synthesis of tricycloclavulone are currently under way.

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5. Compound **5**: IR (neat): ν 1746, 1731, 1294, 747 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.89 (1H, bdd, $J=9.1$, 13.5 Hz), 2.13 (1H, dddd, $J=6.9$, 8.7, 11.9, 13.5 Hz), 2.39 (1H, ddd, $J=1.0$, 8.7, 18.3 Hz), 3.02 (1H, ddd, $J=9.1$, 11.9, 18.3 Hz), 3.67 (1H, d, $J=6.9$ Hz), 3.75 (3H, s), 5.88 (1H, s), 7.26–7.38 (3H, m), 7.49–7.53 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 (CH_2), 34.9 (CH_2), 48.3 (CH), 52.3 (CH_3), 66.2 (C), 128.8 (CH), 129.4 (CH), 129.7 (C), 133.0 (CH), 133.8 (CH), 140.5 (C), 167.6 (C), 208.4 (C); EI-MS *m*/*z*: 274 (M^+). Anal. calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.55; H, 5.11%.
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9. Compound **3**: IR (neat): ν 1721, 1446, 1321, 1155, 1004, 731 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.63–0.71 (6H, m), 0.95–1.00 (9H, m), 1.38–1.53 (1H, m), 1.72 (1H, dd, $J=7.6$, 14.1 Hz), 2.10 (1H, dd, $J=7.0$, 13.3 Hz), 2.38 (1H, dt, $J=7.6$, 13.3 Hz), 2.86 (1H, d, $J=7.6$ Hz), 6.20 (1H, d, $J=5.9$ Hz), 6.83 (1H, d, $J=0.9$ Hz), 7.38 (1H, d, $J=5.9$ Hz), 7.50–7.55 (2H, m), 7.59–7.65 (1H, m), 7.98–8.01 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 6.3 (CH_2), 6.8 (CH_3), 22.2 (CH_2), 35.1 (CH_2), 51.5 (CH), 72.4 (C), 85.1 (C), 128.5 (CH), 128.9 (CH), 133.5 (CH), 135.0 (CH), 140.0 (C), 143.9 (C), 146.9 (CH), 160.2 (CH), 201.3 (C); EI-MS *m*/*z*: 387 ($M^+-CH_2CH_3$); HREIMS calcd for $C_{20}H_{23}O_4SSi$ ($M^+-CH_2CH_3$) 387.1086, found 387.1085.
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