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An ynolate-initiated tandem process giving cyclopentenones: total synthesis of cucumin E

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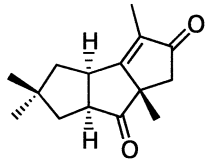
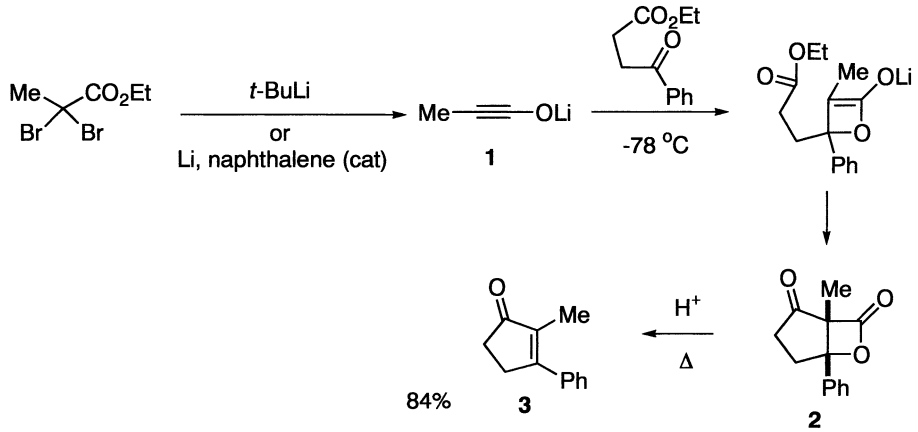
Abstract—A total synthesis of cucumin E, a novel type of triquinane natural product, has been accomplished. The strategy is based on an ynolate-initiated tandem [2+2] cycloaddition–Dieckmann condensation, followed by decarboxylation, giving cyclopentenones. © 2002 Elsevier Science Ltd. All rights reserved.

Since developing a new method for the synthesis of ynolate anions,[1] we have demonstrated their synthetic utility.[2] Recently, we reported a tandem [2+2] cycloaddition–Dieckmann condensation initiated by ynolates (i.e. **1**), followed by decarboxylation of the intermediate bicyclic β-lactones (**2**), to furnish substituted cyclopentenones (**3**) as well as cyclohexanones (Scheme 1).[3] If this novel process were applied to the preparation of carbocyclic frameworks composed of fused five- and six-membered rings, various kinds of natural products, like triquinane sesquiterpenes, could be efficiently synthesized.

Cucumin E (**4**) was isolated from the mycelial cultures of the agaric *Macrocystidia cucumis* (Pers. ex Fr.), and in 1998, its structure and stereochemistry were determined by Steglich and Anke.[4] Linear triquinane-type sesquiterpenoids have aroused a great deal of interest among synthetic chemists in recent decades due to their unique structure and promising biological activity.[5] Many syntheses of these compounds have been reported. However, syntheses of cucumins, which are a new kind of linear triquinane-type sesquiterpenoid, are not as well represented in the literature.[6] We describe herein the total synthesis of cucumin E using an ynolate-initiated tandem reaction for the construction of the cyclopentenone unit.



cucumin E (**4**)



Scheme 1. Ynolate-initiated [2+2] cycloaddition–Dieckmann condensation.

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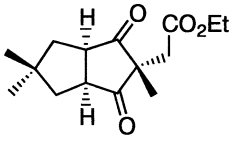
Since cucumin E possesses a 2-cyclopenten-1-one unit, we envisaged the ynolate-initiated tandem reaction of the σ-symmetric bicyclo[3.3.0]octan-2,4-dione (**5**) occuring in the final stage of the total synthesis. First, we attempted the synthesis of the precursor (**5**) directly from the known compound (**7**).



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As shown in Scheme 2, the bicyclic anhydride (**7**), prepared from 4,4-dimethylcyclohexenone according to the literature procedures,[7,8] was reacted with Et_2CuLi to afford the ketocarboxylic acid (**8**). We attempted the Lewis acid-mediated cyclization of the corresponding mixed anhydride and the base induced cyclization of the methyl ester, but failed to obtain the desired bicyclo[3.3.0]octane skeleton (**9**).

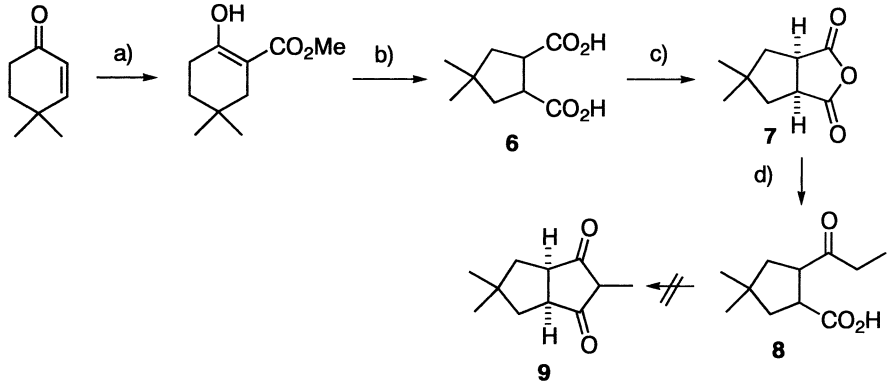
Next, we tried to prepare the precursor (**5**) from 3,4,7,7-tetramethylbicyclo[3.3.0]oct-3-en-2-one (**12**). According to the literature, 4,4-dimethylcyclopentane-1,2-dicarboxylic acid (**6**) was converted to the diketone (**10**) by addition of MeLi which was then cyclized to give the bicyclo[3.3.0]octenone (**11**).[9] This enone was brominated and dehydrobrominated, and the resulting bromoenone was converted to the bromoacetal, which was treated with *t*-BuLi followed by methyl iodide, to provide, after hydrolysis, the enone (**12**).[10] Regioselective alkylation of the dienolate derived from the enone (**12**) was then examined. When the enone was treated with LHMDS and an excess of ethyl bromoacetate was added at room temperature, the undesired γ-alkylation predominated (α:γ = 1:9). Use of KHMDS increased the α-regioselectivity up to 1:1.7. Since counter-cations of the dienolate seemed to influence the regioselectivity, we therefore decided to use NHMDS as a base. When 3 equiv. of ethyl bromoacetate was added to the sodium dienolate, the α/γ ratio was improved to 1:1.2, and after several attempts to find the optimum conditions, the reaction using NHMDS and 16 equiv. of ethyl bromoacetate at room temperature was found to furnish the desired α-alkylated product (**13**) in 45% yield as a single stereoisomer (Scheme 3).[11] The stereochemistry of (**13**), determined by NOE experiments of **5**, can be explained by the attack of the alkylating reagent on the convex face of the dienolate. This compound was subjected to oxidative cleavage of *exo*-olefin to yield the desired diketone (**5**) in 85% yield.[12]

With the diketone (**5**) in hand, we next examined the ynolate-initiated tandem reaction. Under the usual conditions (1.2 equiv. of ynolate at −78 to −40°C), the reaction did not proceed, probably due to steric hindrance of the ketone. However, after screening reaction conditions, using 3 equiv. of ynolates at −20°C for 1 h, we succeeded in obtaining the adduct (**15**), the infrared spectrum of which displays absorptions at 1830 cm^{-1}, indicating the presence of the β-lactone. This adduct was decarboxylated by refluxing in toluene in the presence of silica gel to afford cucumin E (**4**) in 54% yield from the diketone (**5**). The spectral properties were identical in all respects to those of the natural product (^1H and ^{13}C NMR, IR, MS, elemental analysis).[13]

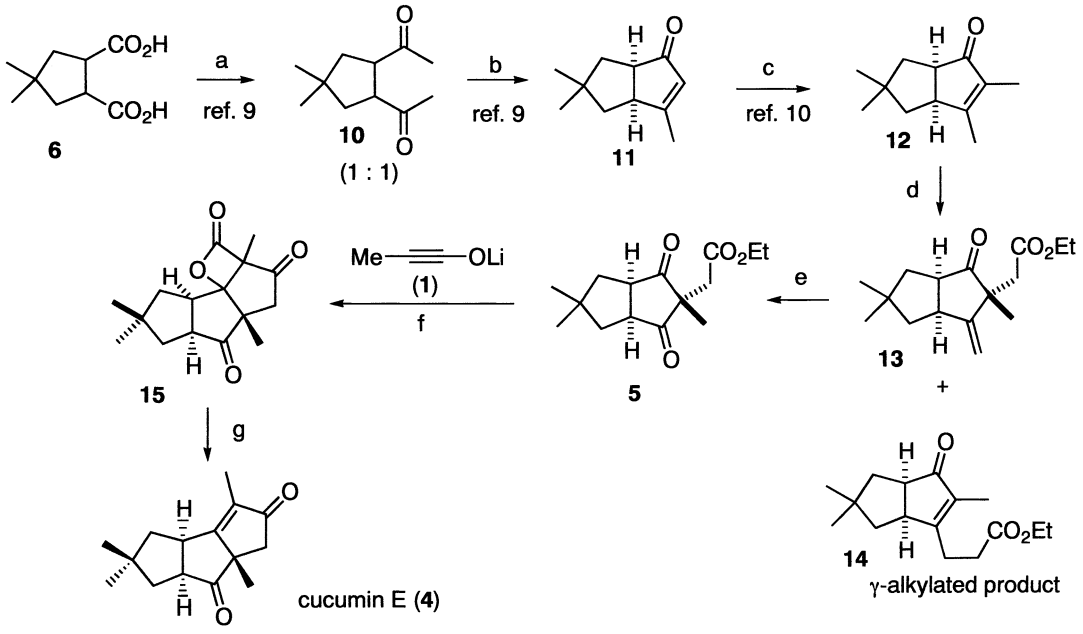
In conclusion, we have achieved a total synthesis of the new triquinane natural product cucumin E. The strategy of five-membered ring construction via ynolate-initiated tandem reaction has demonstrated the feasibility of a short access to triquinane sesquiterpenoids.

Acknowledgements

We are grateful to Professor Steglich for providing us with a sample of natural cucumin E and its spectra. This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas (A) 'Exploitation of Multi-Element Cyclic Molecules' from the Ministry of Education, Culture, Sports, Science and Technology, Japan, and a research grant from the Faculty of Pharmaceutical Sciences, the University of Tokushima.



Scheme 2. *Reagents and conditions*: (a) (i) Pd–C, H_2, AcOEt, rt, 13 h, 98%; (ii) Me_2CO_3 (5.2 equiv.), NaH (2.2 equiv.), DME, reflux, 3 h, 75%; (b) (i) Br_2 (1.0 equiv.), $CHCl_3$, 0°C–rt, 1 h, quant.; (ii) KOH (4.3 equiv.), H_2O, 0°C–rt, 30 h, 87%; (c) Ac_2O (1.1 equiv.), pyridine (4.0 equiv.), toluene, reflux, 60 h, 78%; (d) EtLi (3.0 equiv.), CuI (1.5 equiv.), ether, −40°C, 80%.



Scheme 3. *Reagents and conditions*: (a) MeLi (4.4 equiv.), ether, 0°C–rt, 17 h, 72%; (b) *t*-BuOK (0.2 equiv.), *t*-BuOH, 0°C–rt, 3 h, 78%; (c) (i) Br_2 (1.1 equiv.), CCl_4, 0°C 3 h then Et_3N, 83%; (ii) ethylene glycol (5.0 equiv.), *p*TsOH (0.1 equiv.), benzene, reflux, 70 h, 75%; (iii) *t*-BuLi (3.0 equiv.); MeI (12 equiv.), HMPA (2.9 equiv.), THF, −78°C, 2 h, then 10% HCl, 99%; (d) NHMDS (1.5 equiv.), $BrCH_2CO_2Et$ (16 equiv.), rt, 1.5 h, 45%; (e) $RuCl_3$ (0.1 equiv.), $NaIO_4$ (4.1 equiv.), rt, 10 h, 85%; (f) lithium ynolate (**1**) (3 equiv.), THF, −20°C, 1 h; (g) silica gel (cat.), toluene, reflux, 13 h, 54% for two steps.

References

1. (a) Shindo, M. *Tetrahedron Lett*. **1997**, *38*, 4433–4436; (b) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron* **1998**, *54*, 2411–2422; (c) Shindo, M.; Koretsune, R.; Yokota, W.; Itoh, K.; Shishido, K. *Tetrahedron Lett*. **2001**, *42*, 8357–8360.
2. (a) Shindo, M.; Sato, Y.; Shishido, K. *Tetrahedron Lett*. **1998**, *39*, 4857–4860; (b) Shindo, M.; Oya, S.; Sato, Y.; Shishido, K. *Heterocycles* **1998**, *49*, 113–116; (c) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem*. **2000**, *65*, 5443–5445; (d) Shindo, M.; Oya, S.; Murakami, R.; Sato, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 5943–5946; (e) Shindo, M.; Oya, S.; Murakami, R.; Sato, Y.; Shishido, K. *Tetrahedron Lett*. **2000**, *41*, 5947–5950; (f) Shindo, M.; Matsumoto, K.; Sato, Y.; Shishido, K. *Org. Lett*. **2001**, *3*, 2029–2031. For reviews, see: (g) Shindo, M. *Chem. Soc. Rev*. **1998**, *27*, 367–374; (h) Shindo, M. *J. Syn. Org. Chem. Jpn*. **2000**, *58*, 1155–1166; (i) Shindo, M. *Yakugaku Zasshi* **2000**, *120*, 1233–1246.
3. (a) Shindo, M.; Sato, Y.; Shishido, K. *J. Am. Chem. Soc*. **1999**, *121*, 6507–6508; (b) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem*. **2001**, *66*, 7818–7824.
4. Hellwig, V.; Dasenbrock, J.; Schumann, S.; Steglich, W.; Leonhardt, K.; Anke, T. *Eur. J. Org. Chem*. **1998**, 73–79.
5. The first total synthesis of cucumin E: Mehta, G.; Umarye, J. D. *Tetrahedron Lett*. **2001**, *42*, 1991–1993.
6. For reviews, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev*. **1997**, *97*, 671–719; (b) Singh, V.; Thomas, B. *Tetrahedron* **1998**, *54*, 3647–3692.
7. Liu, H.-J.; Browne, E. N.; Chew, S. Y. *Can. J. Chem*. **1988**, *66*, 2345–2347.
8. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem*. **1989**, *54*, 817–824.
9. Miyano, K.; Ohfune, Y.; Azuma, S.; Matsumoto, T. *Tetrahedron Lett*. **1974**, 1545–1548.
10. (a) Tobe, Y.; Yamashita, D.; Takahashi, T.; Inata, M.; Sato, J.; Kakiuchi, K.; Kobiro, K.; Odaira, Y. *J. Am. Chem. Soc*. **1990**, *112*, 775–779; (b) Smith, A. B.; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth. Coll. Vol. VII* **1990**, 271–275.
11. The γ-alkylated product was also isolated in 47% yield.
12. Diketone (**5**): ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.00 (3H, s), 1.11 (3H, s), 1.19 (3H, s), 1.20 (3H, t, $J=7.2$ Hz), 1.56 (2H, m), 2.08 (2H, m), 2.91 (2H, s), 3.55 (2H, ddd, $J=2.8$, 4.4, 10.0 Hz), 4.03 (2H, q, $J=6.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.0 (q), 22.7 (q), 26.0 (q), 28.0 (q), 42.6 (t), 43.2 (s), 45.1 (t), 52.8 (d), 53.3 (s), 61.4 (t), 171.3 (s), 219.3 (s). IR ($CHCl_3$): 1762, 1713 cm^{-1}. MS *m*/*z*: 266 (M^+), 267 (M+1), 193 (M^+–$COOCH_2CH_3$, 100%). HRMS (EI) calcd for $C_{15}H_{22}O_4$ (M^+) 266.1518, found: 266.1514.
13. Mp 121.3–121.8°C (hexane) for racemic form (lit., mp 108°C for optically pure form).