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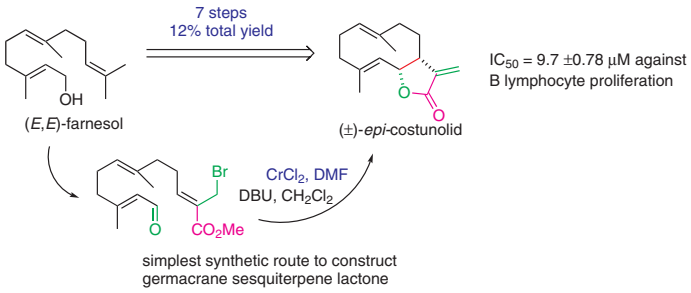
Efficient Construction of (±)-*epi*-Costunolide through a Chromium(II)-Mediated Nozaki–Hiyama–Kishi Reaction

Weichen Dai[a,b]
Jie Zheng[a]
Xinyu Yan[a]
Wei Tang[c]
Lihong Hu[*a]
Yinan Zhang[*a]

[a] Jiangsu Key Laboratory for Functional Substances of Chinese Medicine, School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, 210023, P. R. of China
yinanzhang@njucm.edu.cn
lhhu@njucm.edu.cn
[b] Hanlin College, Nanjing University of Chinese Medicine, Taizhou 225300, P. R. of China
[c] Pharmaron (Ningbo) Technology Development Co., Ltd, Ningbo, 315336, P. R. of China



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Abstract (±)-*epi*-Costunolide has been synthesized through a seven-step procedure starting from (*E*,*E*)-farnesol. The key step includes an intramolecular allylation of an aldehyde through a chromium(II)-mediated Nozaki–Hiyama–Kishi reaction, in which more than one equivalent of $CrCl_2$ has been recognized as the most effective reagent to promote the conversion. An anti-inflammatory screen showed that *epi*-costunolide is a moderate inhibitor of B lymphocyte proliferation.

Key words costunolide, germacrenes, Nozaki–Hiyama–Kishi reaction, total synthesis, medicinal chemistry, sesquiterpenoid lactones

Costunolide is a germacrene sesquiterpene lactone isolated from the herbal preparation radix aucklandiae, obtained from the roots of *Saussurea costus* (formerly *Aucklandia lappa* Decne), that shows a wide variety of pharmacological activities including antiinflammatory,[1] antibacterial,[2] and antitumor properties.[3] Costunolide has a ten-membered-ring skeleton fused to a *trans* α-methylene γ-lactone at the C6 and C7 positions. Owing to its simple structure and unique activities, costunolide has received much attention from the synthetic and medicinal communities. Although its structural modifications and structure–activity relationship have been extensively studied,[4] only a few synthetic approaches have focused on the construction of the germacrene scaffold. The challenges mostly lie in (1) the formation of a medium-sized ring, (2) stereochemical control, and (3) structurally sensitivity to both acidic and basic conditions.

The first total synthesis was carried out by Grieco and Nishizawa,[5] who employed α-santonin as the starting material and a Cope sigmatropic rearrangement to expand to the ten-membered ring (Scheme 1a). In contrast, Takahashi et al. contracted a 13-membered cyclic ether ring through a [2,3]-Wittig rearrangement to afford a germacrene scaffold (Scheme 1b).[6] Another synthesis by Yang et al.[7] featured an aldol addition of chiral camphorsultam derivative to an α,β-unsaturated aldehyde (Scheme 1c). Refunctionalization, C8–C9 intramolecular alkylation, and oxidative lactonization gave costunolide in a total of 13 reaction steps. The most efficient synthetic strategy came from a bioinspired cyclization of an aldehyde and allylic halide, which included a Nozaki–Hiyama–Kishi (NHK) reaction or a Barbier reaction developed by Hirotaka et al.,[8] and by Corey and Reddy,[9] respectively (Scheme 1d). The configuration of the *anti*-adduct was controlled by a Zimmerman–Traxler transition state. However, further conversions into the γ-lactone still required an allylic oxidation involving highly flammable *t*-BuLi and an extra esterification. Toward this end, we have developed an efficient strategy for the construction of the germacrene scaffold and the corresponding total synthesis of (±)-*epi*-costunolide. This synthetic method sets the stage for future in-depth structure–activity relationship studies and mechanistic investigations of this fascinating natural product.

Our initial intent was to utilize the lactone ring with a preassembled ester group on the farnesol chain. Compared with the existing strategy, our current retrosynthetic format features a tandem allylation reaction and a lactonization to give costunolide in a one-pot procedure (Scheme 2). The ester intermediate **1** might be obtained by an allylic S_N' substitution and a Baylis–Hillman reaction from aldehyde **3**, which, in turn, could be simply obtained by direct oxidation from (*E*,*E*)-farnesol.

Since the key step is the tandem allylation and lactonization, we attempted a template reaction between 3-methylcrotonaldehyde (**5**) and the Baylis–Hillman ester **6**. First, we screened the general conditions previously studied for either the Barbier or the NHK reaction (Table 1). To our delight, more than one equivalent of $CrCl_2$ in DMF gave the

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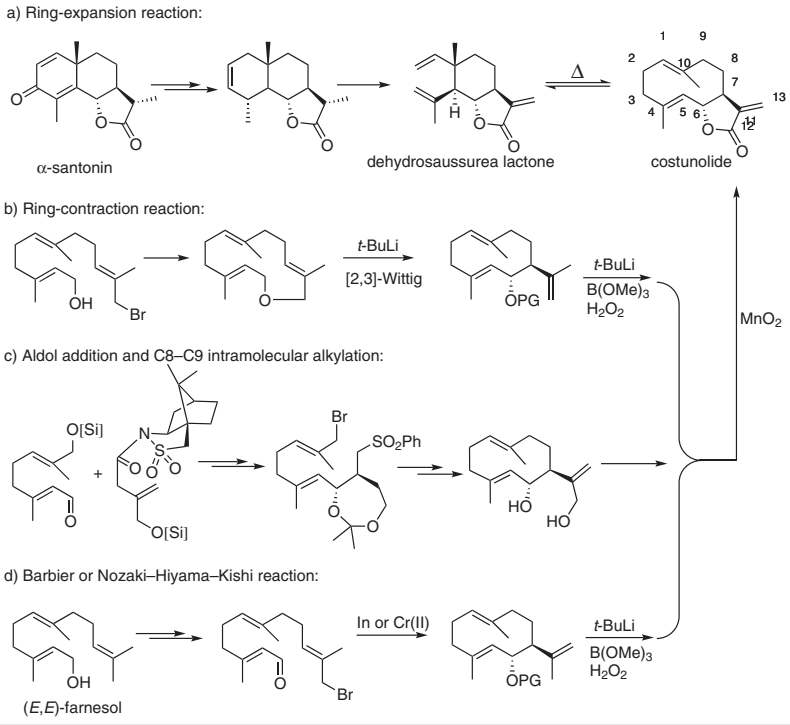


Scheme 1 Reported syntheses of costunolide

syn-product **7** in 82% yield (Table 1, entry 1). However, none of the corresponding product was detected when chromium(II) was generated in situ with $LiAlH_4$ (entry 2). Note that a catalytic amount of $CrCl_2$ with Mn(0)[10] also gave the desired product, albeit in a low yield (entry 3). Since the NHK reaction did not directly give the *anti*-lactone product, we next tried several standard conditions for the Barbier reaction. Zero-valent metals such as In,[11] Zn,[12] or Zn–Cu[12] afforded the *syn*-lactone product **8** in good to moderate yields (entries 4–6). Unfortunately, an extensive search of conditions showed that no metal exclusively gave the desired *anti*-lactone product **9** in a satisfactory yield (entries 7 and 8). Other conditions with various Sn salts failed to give the desired product (entry 9).[13]

A plausible mechanism for the metal-mediated carbonyl allylation is proposed in Figure 1. Initially, a metal–halogen exchange activates the Baylis–Hillman ester **6**, and the activated ester undergoes coordination to the acrylate **5**. The (*Z*)-allyl intermediate that produces the *syn*-product adopts a chair transition state, whereas the formation of the (*E*)-allyl intermediate requires a boat transition state, which hinders the production of the *anti*-product. Tin could have produced a mixture of *syn*- and *anti*-products as a result of instability of the allyltin toward *Z*–*E* isomerization.[14]

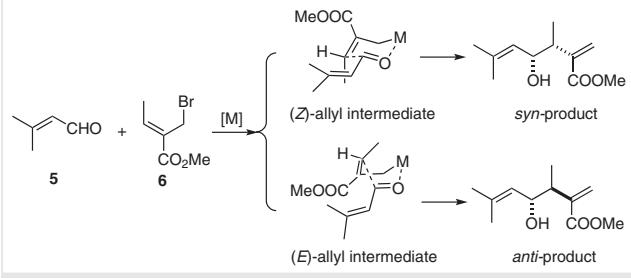
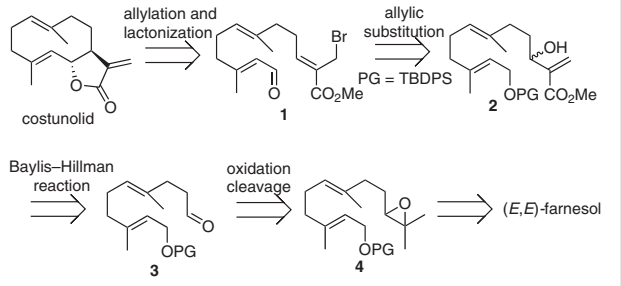


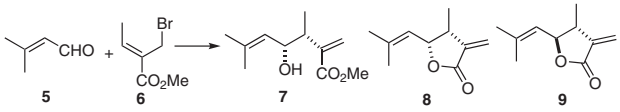
Figure 1 A plausible mechanism for the carbonyl allylation.



Scheme 2 Retrosynthetic analysis of costunolide synthesis

With the optimal conditions for the allylation in hand, we made a further attempt at a total synthesis (Scheme 3) starting with TBDPS protection and epoxidation of (*E*,*E*)-farnesol on a gram scale (49% overall yield). Periodate oxidation of **4** afforded the desired aldehyde **3** in an excellent yield. Note that a TBS protective group was not stable to periodate oxidation, whereas TBDPS survived this. Use of the standard Baylis–Hillman conditions successfully added the acrylate moiety to the scaffold, which was converted into the allylic bromide **10** in the presence of PPh_3 and CBr_4.

Table 1 Optimization of a Template Carbonyl Allylation[a]

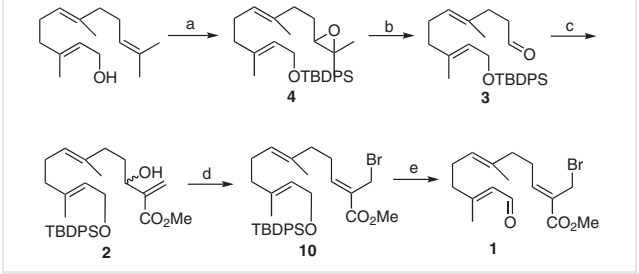


Entry	Conditions	Equiv	Solvent	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	$CrCl_2$	7	DMF	rt	5	**7**	82
2	$CrCl_3$/Li-AlH_4	8/4	DMF	rt	5	–	–[c]
3	$CrCl_2$/Mn	0.1/2	DMF	rt	8	**7**	8
4	In	2	DMF	rt	4	**8**	56
5	Zn	6	THF	65	10	**8**	51
6	Zn–Cu	6	THF	rt	1	**8**	79
7	$SnCl_2$/KI	1.5/1.5	THF	rt	18	**8**, **9**	16, 25[d]
8	Sn	2	THF–aq NH_4Cl (2:1)	60	12	**7**, **8**, **9**	20, 7, 13[d]
9	Sn-Cl_4/TBAI	2/6	CH_2Cl_2	rt	48	–	–[e]

[a] All reactions were conducted under an argon atmosphere. 3-Methylcrotonaldehyde (**5**) reacted with the Baylis–Hillman ester **6** in a ratio of 1:2; see the Supporting Information for details.
[b] Isolated yield unless specified.
[c] Decomposition of the starting material.
[d] **8** and **9** were inseparable by silica gel chromatography, and their yields were determined by ^1H NMR spectroscopy of the mixture.
[e] No product was detected.

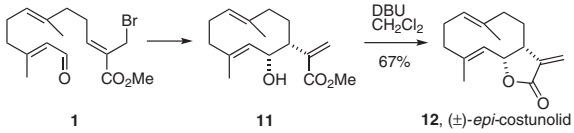
The precursor **1** was obtained by Dess–Martin oxidation after removal of the TBDPS group in a HF/pyridine medium. The overall yield of this five-step conversion was, remarkably, as high as 24%.

By using our optimized conditions, precursor **1** was treated with $CrCl_2$ in DMF to give the homoallylic alcohol *syn*-product **11** in a comparable yield to that of the NHK template reaction.[15] However, zero-valent metals under Barbier conditions decomposed compound **1** and failed to deliver the desired lactone product directly under the optimal reaction conditions (Table 2). Finally, an intramolecular cyclization was carried out with DBU to give (±)-*epi*-costunolide **12**, the relative configuration of which was revealed by NOE spectroscopy (see the Supporting Information). Note also that Massanet's group previously obtained *epi*-costunolide by a semi-synthesis from natural costunolide;[16] however, our method is based on an ab initio synthetic route.



Scheme 3 Synthesis of precursor **1**. *Reagents and conditions*: (a) (i) TBDPSCl, imidazole, CH_2Cl_2; (ii) NBS, THF–H_2O (3:1); (iii) K_2CO_3, MeOH; 49% for three steps; (b) H_5IO_6, $NaIO_4$, THF–H_2O (4:1), 95%; (c) methyl acrylate, DABCO, MeOH, 81%; (d) CBr_4, Ph_3P, DIPEA, CH_2Cl_2, 86%; (e) (i) HF–pyridine, THF, 84%; (ii) Dess–Martin periodinane, CH_2Cl_2, 87%.

Table 2 Completion of the (±)-*epi*-Costunolide (**12**) Synthesis[a]



Entry	Conditions	Equiv	Solvent	Temp (°C)	Time (h)	Yield[b] (%) of **11**
1	$CrCl_2$	7	DMF	rt	3	76
2	In	2	DMF	rt	5	–[c]
3	Zn	6	THF	65	10	–[c]
4	Zn–Cu	6	THF	rt	10	–[c]

[a] All reactions were conducted under an argon atmosphere; see the Supporting Information for details.
[b] Isolated yield.
[c] Decomposition of compound **1**.

Biological studies showed that the epimer (IC_{50}: 9.7 ± 0.78 μM) had a weaker antiinflammatory effect than natural costunolide (IC_{50}: 1.2 ± 0.19 μM) in inhibiting B lymphocyte proliferation.

In summary, a robust and effective route including a key intramolecular cyclization reaction with $CrCl_2$ readily afforded (±)-*epi*-costunolide. Starting from (*E*,*E*)-farnesol, this is the simplest synthetic route to date for constructing a germacrane sesquiterpene lactone, requiring only seven steps and giving a 12% total yield. Considering its high stereoselectivity, the chromium(II)-mediated NHK reaction has proven to be a convenient method for the synthesis of further analogues of use in a medicinal perspective; these are under development in our laboratory and will be reported in due course.

Conflict of Interest

The authors declare no conflict of interest.

Funding Information

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ural Science Foundation of the Jiangsu Higher Education Institutions of China (grant: 18KJD360001).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1720348.

References and Notes

(1) (a) Scarponi, C.; Butturini, E.; Sestito, R.; Madonna, S.; Cavani, A.; Mariotto, S.; Albanesi, C. *PLoS One* **2014**, *9*, e107904. (b) Zheng, H.; Chen, Y.; Zhang, J.; Wang, L.; Jin, Z.; Huang, H.; Man, S.; Gao, W. *Chem.–Biol. Interact.* **2016**, *250*, 68.

(2) (a) Luna-Herrera, J.; Costa, M.; González, H.; Rodrigues, A.; Castilho, P. *J. Antimicrob. Chemother.* **2007**, *59*, 548. (b) Park, J.-B.; Lee, C.-K.; Park, H.-J. *Arch. Pharmacal Res* **1997**, *20*, 275. (c) Duraipandiyan, V.; Al-Harbi, N. A.; Ignacimuthu, S.; Muthukumar, C. *BMC Complementary Altern. Med.* **2012**, *12*, 13.

(3) (a) Bocca, C.; Gabriel, L.; Bozzo, F.; Miglietta, A. *Chem.–Biol. Interact.* **2004**, *147*, 79. (b) Cai, H.; He, X.; Yang, C. *Phytother. Res.* **2018**, *32*, 1764. (c) Dong, G.-Z.; Shim, A.-R.; Hyeon, J. S.; Lee, H. J.; Ryu, J.-H. *Phytother. Res.* **2015**, *29*, 680. (d) Hsu, J.-L.; Pan, S.-L.; Ho, Y.-F.; Hwang, T.-L.; Kung, F.-L.; Guh, J.-H. *J. Urol (N. Y., NY U. S.)* **2011**, *185*, 1967. (e) Liu, C.-Y.; Chang, H.-S.; Chen, I.-S.; Chen, C.-J.; Hsu, M.-L.; Fu, S.-L.; Chen, Y.-J. *Radiat. Oncol.* **2011**, *6*, 56.

(4) (a) Macías, F. A.; Galindo, J. C. G.; Massanet, G. M. *Phytochemistry* **1992**, *31*, 1969. (b) Barrero, A. F.; Oltra, J. E.; Cuerva, J. M.; Rosales, A. *J. Org. Chem.* **2002**, *67*, 2566. (c) Macías, F. A.; Velasco, R. F.; Álvarez, J. A.; Castellano, D.; Galindo, J. C. G. *Tetrahedron* **2004**, *60*, 8477. (d) Srivastava, S. K.; Abraham, A.; Bhat, B.; Jaggi, M.; Singh, A. T.; Sanna, V. K.; Singh, G.; Agarwal, S. K.; Mukherjee, R.; Burman, A. C. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4195. (e) Vadaparthi, P. R. R.; Kumar, C. P.; Kumar, K.; Venkanna, A.; Nayak, V. L.; Ramakrishna, S.; Babu, K. S. *Med. Chem. Res.* **2015**, *24*, 2871.

(5) Grieco, P. A.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717.

(6) Takahashi, T.; Nemoto, H.; Kanda, Y.; Tsuji, J.; Fujise, Y. *J. Org. Chem.* **1986**, *51*, 4315.

(7) Yang, Z.-J.; Ge, W.-Z.; Li, Q.-Y.; Lu, Y.; Gong, J.-M.; Kuang, B.-J.; Xi, X.; Wu, H.; Zhang, Q.; Chen, Y. *J. Med. Chem* **2015**, *58*, 7007.

(8) Hirotaka, S.; Kazuyoshi, O.; Keiko, K.; Kazuyuki, H.; Nobutoshi, M.; Isao, K. *Chem. Lett.* **1986**, 85.

(9) Reddy, D. S.; Corey, E. J. *J. Am. Chem. Soc.* **2018**, *140*, 16909.

(10) Fürstner, A.; Shi, N. *J. Am. Chem. Soc* **1996**, *118*, 12349.

(11) Bryan, V. J.; Chan, T.-H. *Tetrahedron Lett.* **1996**, *37*, 5341.

(12) Semmelhack, M. F.; Wu, E. S. C. *J. Am. Chem. Soc* **1976**, *98*, 3384.

(13) Masuyama, Y.; Suga, T.; Watabe, A.; Kurusu, Y. *Tetrahedron Lett* **2003**, *44*, 2845.

(14) (a) Verdone, J. A.; Mangravite, J. A.; Scarpa, N. M.; Kuivila, H. G. *J. Am. Chem. Soc* **1975**, *97*, 843. (b) Matarasso-Tchiroukhine, E.; Cadiot, P. *J. Organomet. Chem.* **1976**, *121*, 155.

(15) **Intramolecular Allylation of Compound 1**
A solution of the aldehyde **1** (94 mg, 0.273 mmol) in anhyd DMF (2.5 mL) was added to a solution of $CrCl_2$ (235 mg, 1.9 mmol) in anhyd DMF (12 mL) at rt under Ar. The mixture was stirred for 3 h and then the reaction was quenched with H_2O (8 mL). The mixture was extracted with EtOAc, and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under a reduced pressure. The residue was purified by column chromatography (silica gel, 5% EtOAc–hexane) to give **11** as a colorless oil; yield: 54.5 mg (0.208 mmol, 76%).
^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.36–6.29 (m, 1 H), 5.78–5.74 (m, 1 H), 5.13–4.98 (m, 2 H), 4.41–4.40 (m, 1 H), 3.80 (s, 3 H), 2.76–2.52 (m, 2 H), 2.43–2.33 (m, 2 H), 2.22–2.19 (m, 1 H), 2.13 (d, *J* = 9.3 Hz, 3 H), 2.02–1.84 (m, 1 H), 1.78–1.69 (m, 2 H), 1.59 (s, 3 H), 1.44–1.40 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.7, 142.7, 138.7, 137.4, 126.7, 124.3, 122.1, 70.3, 52.2, 44.3, 40.0, 37.3, 34.9, 25.6, 21.0, 17.0. HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{16}H_{24}NaO_3$: 287.1623; found: 287.1618

(16) Azarken, R.; Guerra, F. M.; Moreno-Dorado, F. J.; Jorge, Z. D.; Massanet, G. M. *Tetrahedron* **2008**, *64*, 10896.