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Concise synthesis of a highly functionalized cyclopentane segment: toward the total synthesis of kansuinine A

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Abstract—Kansuinine A, isolated from the plant *Euphorbia kansui Liou*, is one of a series of jatrophane diterpenes that have novel structural features, which include contiguous stereocenters, a highly oxygenated carbon framework, and a tricyclic ring system. We describe here a short and concise synthesis of the cyclopentane segment of kansuinine A via SmI_2-mediated cyclization of δ-iodo-ester as a key construction method.

Naturally occurring jatrophane diterpenes, which contain many stereocenters and hydroxyl moieties acylated with Ac, Bz, Nic (nicotinoyl) groups as common features, have been found in several plants of *Euphorbia* sp. While we now have access to many of these diterpenes, some of these may require more attention.[1] Euphosalicin and pepluanins are novel jatrophane diterpenes that significantly inhibited the p-Gp-triggered efflux pump. A jatrophane isolated from *E. semiperfoliata* has been shown to interact with microtubule, not in a paclitaxel-like pathway but rather by influencing p53 expression and Raf-1/Bcl-2 activation. These are promising candidates for anti-tumor therapeutic agents. Recently, Multzer and co-workers[2] and Hiersemann and co-workers[3] reported synthetic studies toward these compounds. However, the total synthesis of fully functionalized jatrophane diterpenes has not been achieved.

Kansuinine A (**1**), which was isolated from the plant *Euphorbia kansui Liou* in 1975, is a unique jatrophane diterpene with contiguous stereocenters, high oxygenation, acylation, and a tricyclic ring framework.[4] We selected **1** as a synthetic target based on its fascinating and ultimately complex structure. Moreover, **1** exhibits novel biological activities such as analgesic activity and induction of neuron growth factor (NGF) production.[5] These facts also inspired us to wrestle with the synthesis of **1**.

Our synthetic plan is outlined in Figure 1. We envisaged that the macrocyclic framework of **1** could be constructed via two key couplings: Nozaki–Hiyama–Kishi (NHK) coupling as the 1st step between C5 of aldehyde **2** (segment A) and C6 of vinyl iodide **3** (segment B) and NHK coupling as the 2nd step between C12 and C13 could generate compound **4**.

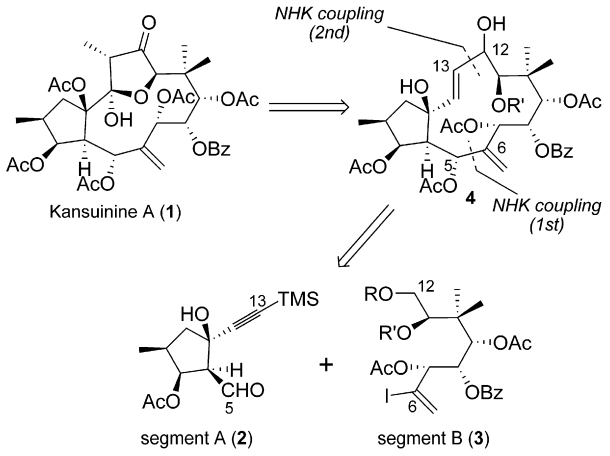

Figure 1. Retrosynthetic analysis of kansuinine A (**1**).

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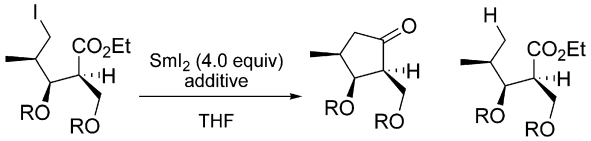
The final tetrahydrofuran ring formation may make it possible to achieve the total synthesis of **1**. Thus, we set our initial goal as the stereoselective synthesis of **2**.

The synthesis of **2** began with the Mukaiyama aldol reaction of ethyl *C*,*O*-bis(trimethylsilyl)ketene acetal and known aldehyde **6**,[6] which was easily prepared from commercially available chiral hydroxyester **5**, to produce aldol adduct (Scheme 1).[7] Sequential desilylation by treatment with KF gave β-hydroxyester **7** with high enantioselectivity. For the next diastereoselective alkylation,[8] enolate dianion of **7** was generated by the addition of LDA (2.2 equiv). It was then reacted with anhydrous formaldehyde solution in ether[9] to install the hydroxymethyl moiety in diol **8** with an *anti* preference (*anti*:*syn* = 78:22).[10] The diol moiety of **8** was protected with the isopropylidene group to produce both *anti*- and *syn*-**9** as chromatographically separable compounds. The stereochemistry of the desired *anti*-**9** was confirmed by an NOE experiment. Finally, cleavage of the Bn group of *anti*-**9** and sequential iodination of the resulting primary alcohol provided δ-iodoester **10**.

For a fast and efficient construction of the cyclopentane ring, we thought that it might be possible to use the samarium(II) iodide (SmI_2)-mediated intramolecular nucleophilic acyl substitution of δ-halo esters. This type of reaction was previously discovered by Molander's group.[11] However, only a few applications utilizing halo esters have been reported.[12,13] Thus, the SmI_2-mediated cyclizations of δ-iodoester were first screened for both substrates (including **10**)[14] and additives to increase the reduction potential of the samarium species (Table 1).[15] As a result, the reaction performed using acetonide derivative **10**, SmI_2 (4.0 equiv) and a catalytic amount of $Fe(acac)_3$ (4 mol %)[16] was found to be the most effective

Table 1. Screening for samarium(II) iodide (SmI_2)-mediated cyclization of δ-iodoesters



10 R = -C(Me)$_2$- **11** R = H **12** R = TBS

13 R = -C(Me)$_2$- **15** R = H **17** R = TBS **14** R = -C(Me)$_2$- **16** R = H **18** R = TBS

Substrate	Additive (4 mol %)	Conditions	Products	
			Cyclized	Protonated
10	$Fe(acac)_3$	rt, 3 h	**13**[a] (38%)	Trace
10	$Fe(DBM)_3$	rt, 2 h	—	—
10	HMPA[b]	−30 °C to 0 °C, 3 h	**13**[c] (27%)	Trace
11[d]	$Fe(acac)_3$	rt, 1 h	—	**16** (21%)[e]
12	$Fe(acac)_3$	rt, 2 h	**17** (36%)	**18** (28%)

All reactions were carried out on a 0.05 mmol-scale using SmI_2 (4.0 equiv, 0.1 M solution) unless otherwise noted.

[a] 49% of starting material **10** was recovered.

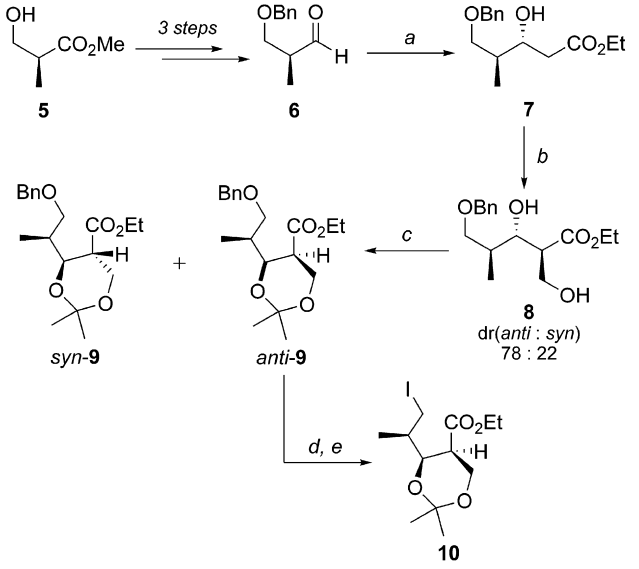
[b] 6.0 equiv of HMPA was used.

[c] 57% of **10** was recovered.

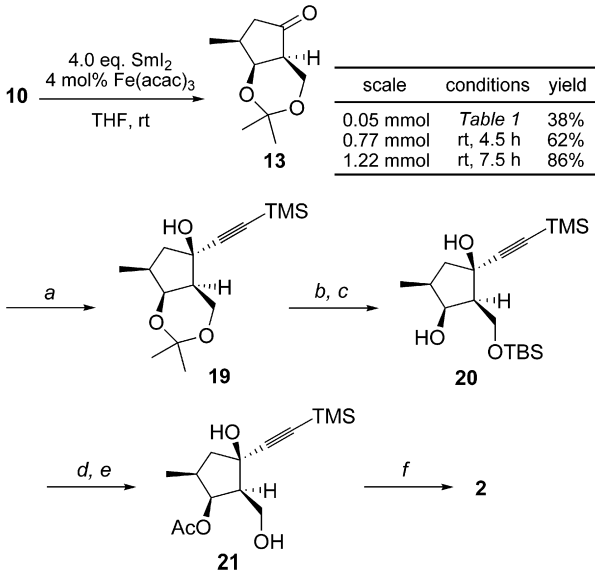
[d] Reaction was conducted with 2.0 equiv of SmI_2 and 2 mol % of additive.

[e] 44% of **12** was recovered.

and provided the desired cyclopentanone **13**[17] in 38% yield. Though the yield of compound **13** was low under screening conditions (0.05 mmol), it was improved by performing the reaction on a larger scale; up to 86% yield on a 1.22 mmol scale (Scheme 2). However, the reaction of diol **11** gave only protonated product **15** as expected. Additionally, bis-TBS ether **12** gave mixtures of cyclized product **17** (36%) and protonated product **18** (28%).



Scheme 1. Synthesis of δ-iodoester **10**. Reagents and conditions: (a) (i) ethyl *C*,*O*-bis(trimethylsilyl)ketene acetal, $TiCl_4$, CH_2Cl_2, −78 °C; K_2CO_3 aq; (ii) KF, 80% MeOH aq, rt, 72%; (b) LDA, CH_2O in Et_2O (ca. 1.0 M), THF, −30 °C, 78% (*anti*:*syn* = 78:22); (c) 2,2-dimethoxypropane, CSA, acetone, rt, *anti*-**9** (75%), *syn*-**9** (21%); (d) H_2, Pd/C, MeOH, rt, 99%; (e) I_2, PPh_3, imidazole, benzene, rt, 95%.



Scheme 2. Conversion to segment A (**2**). Reagents and conditions: (a) trimethylsilylethynylmagnesium bromide, THF, 0 °C, 73%; (b) CSA, MeOH–H_2O, rt, quant.; (c) TBSCl, imidazole, DMAP, DMF, rt; (d) Ac_2O, NEt_3, DMAP, rt; (e) CSA, MeOH, rt, 77% (three steps); (f) Dess–Martin periodinane, CH_2Cl_2, rt, quant.

The final conversion to segment A (**2**) is shown in Scheme 2. It began with a nucleophilic attack of trimethylsilylethynylmagnesium bromide to **13** to generate tertiary alcohol **19** as a single stereoisomer. Deprotection of the isopropylidene group and protection of the derived primary hydroxyl moiety with the TBS group afforded diol **20**. The secondary hydroxyl moiety of **20** was protected with the Ac group. Subsequent deprotection of the TBS group yielded primary alcohol **21**. Final conversion was achieved by Dess–Martin oxidation[18] of **21** to produce **2**.[19]

In summary, segment A (**2**) was prepared in 12 steps from **6**. The synthesis of **2** features stereo-controlled and rapid access to the fully functionalized cyclopentane framework and its construction via the SmI_2-mediated cyclization of δ-iodoester. These findings should help us to achieve the first total synthesis of kansuinine A (**1**) and related jatrophane diterpenes.

Acknowledgements

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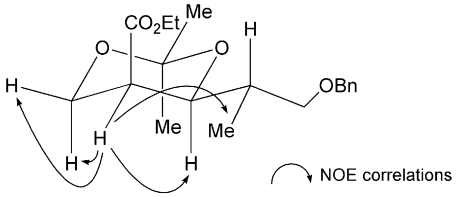
10. The *anti*:*syn* ratio of diol **8** was determined by integration ratio in ^1H NMR spectrum. Their stereochemistry were confirmed by NOE experiments of the corresponding acetonide derivative **9**. NOE correlations of *anti*-**9** was shown below.



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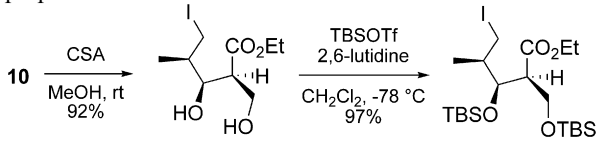
13. For selected reviews of SmI_2-mediated reactions, see (a) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307; (b) Krief, A.; Laval, A.-M. *Chem. Rev.* **1999**, *99*, 745; (c) Edmonds, D. J.; Johnston, D.; Procter, D. J. *Chem. Rev.* **2004**, *104*, 3371.
14. The substrates, diol **11** and bis-TBS ether **12** were prepared as shown below.



15. We also tried the intramolecular acyl substitution of **10** with *t*-BuLi (with or without TMSCl), however, complex mixtures were given. For the references of this reaction, see: (a) van der Does, T.; Klumpp, G. W.; Schakel, M. *Tetrahedron Lett.* **1986**, *27*, 519; (b) Kim, D.; Lee, Y. K. *Tetrahedron Lett.* **1991**, *32*, 6885.
16. For SmI_2-mediated reactions using Fe(III) as additives, see Refs. 11 and 13b.
17. Spectroscopic data of **13**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (d, $J = 6.0$, 3H), 1.30 (s, 3H), 1.46 (s, 3H), 1.98 (d, $J = 3.6$, 4.0, 1H), 2.13 (dd, $J = 11.4$, 17.2, 1H), 2.24 (m, 1H), 2.37 (dd, $J = 7.2$, 17.2, 1H), 4.03 (dd, $J = 4.4$, 12.0, 1H), 4.20 (dd, $J = 1.6$, 12.0, 1H), 4.42 (dd, $J = 3.6$, 3.6, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) 13.3, 18.8, 29.1, 34.7, 42.3, 48.9, 56.9, 71.3, 97.4, 217; HRMS (FAB) calcd for $C_{10}H_{17}O_3$ [$(M+H)^+$] 185.1178. Found: 185.1199.
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19. Spectroscopic data of **2**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H), 1.02 (d, $J = 6.8$, 3H), 1.99 (dd, $J = 10.0$, 13.9, 1H), 2.07 (s, 3H), 2.40 (m, 1H), 2.56 (dd, $J = 8.8$, 13.9, 1H), 3.15 (d, $J = 5.1$, 1H), 3.46 (s, 1H), 5.68 (dd, $J = 4.9$, 5.1, 1H), 9.78 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.28, 13.8, 20.6, 36.5, 49.7, 65.8, 73.8, 86.4, 108, 185, 199; HRMS (FAB) calcd for $C_{14}H_{23}O_4Si$ [$(M+H)^+$] 283.1365. Found: 293.1342.