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Total Synthesis of the Sesquiterpene (±)-Illudin C via an Intramolecular Nitrile Oxide Cycloaddition

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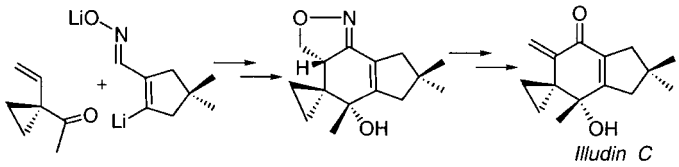
ABSTRACT



A convergent total synthesis of illudin C is described. The tricyclic ring system of the natural product was quickly assembled from cyclopropane and cyclopentene precursors via a novel oxime dianion coupling reaction and a subsequent intramolecular nitrile oxide–olefin cycloaddition.

The illudins are an intriguing class of sesquiterpenes isolated from several fungi.[1] Their varied substitution patterns are suggestive of nature's attempts to optimize their cytotoxic properties. These natural products can be structurally categorized according to the degree and position of unsaturation in the unusual tricyclic ring system and the site of tertiary hydroxyl substituents. Three different types of illudins result from this analysis (Figure 1). Thus, illudin M/S embody a conjugated C(4)−C(5)−C(9)−C(8) diene and C(2) tertiary hydroxyl, whereas an unconjugated C(5)−C(9), C(2)−C(10) diene and C(4) tertiary hydroxyl are found in the illudin C/C_2/C_3 and illudinic acid group. Illudin A/B share features common to both of the aforementioned groups, namely, C(2) and C(4) tertiary hydroxyl substituents and C(5), C(9) sp^2-hybridized carbon atoms.

The cytotoxicity and anticancer activity of illudin S has been most extensively investigated.[2] The target of the compound is believed to be DNA, although an illudin−DNA adduct has yet to be isolated since illudin S does not spontaneously bind to DNA. It has been proposed that illudin S is bioactivated, perhaps by conjugate addition of an endogenous nucleophile (glutathione/NADH)[2b] to the enone moiety. The resultant labile cyclohexadienol intermediate then undergoes facile nucleophilic attack by DNA (or other

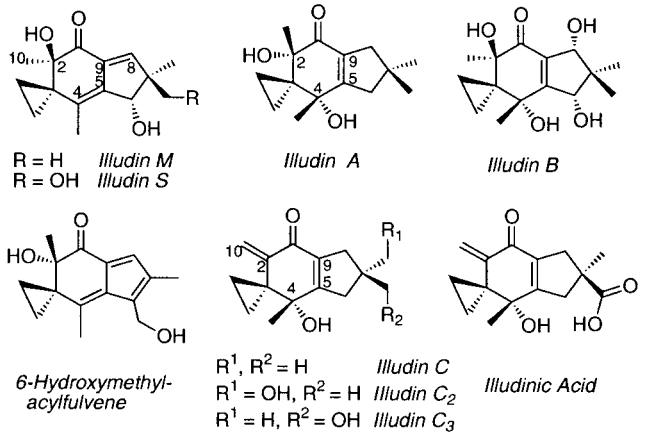


Figure 1.

(1) (a) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Fukuoka, Y.; Takahashi, Y.; Mori, Y.; Watanabe, M. *Tetrahedron* **1965**, *21*, 2671. (b) Arnone, A.; Cardillo, R.; Nasini, G.; de Pava, O. V. *J. Chem. Soc., Perkin Trans. 1* **1991**, 733. (c) Arnone, A.; Cardillo, R.; Modugno, V.; Nasin, G. *Gazz. Chim. Ital.* **1991**, *121*, 345. (d) Lee, I.-K.; Jeong, C. Y.; Cho, S. M.; Yun, B. S.; Kim, Y. S.; Yu, S. H.; Koshino, H.; Yoo, I. D. *J. Antibiot.* **1996**, *49*, 821. (e) Dufresne, C.; Young, K.; Pelaez, F.; Gonzalez, A.; Valentino, D.; Graham, A.; Platas, F.; Bernard, A.; Zink, D. *J. Nat. Prod.* **1997**, *60*, 188.

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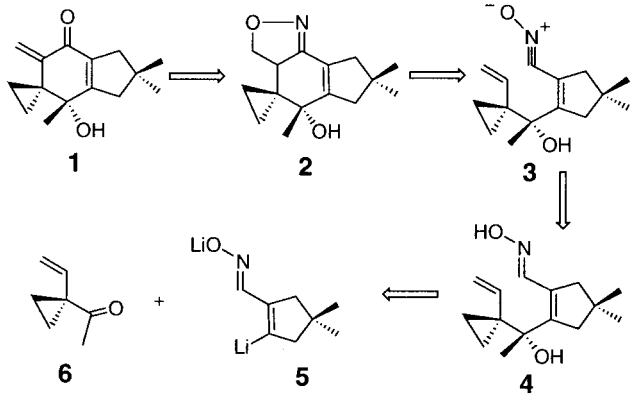
biological targets) on the cyclopropane ring to produce a stable aromatic compound.[3] The low therapeutic index of illudin S has precluded its development as a chemotherapeutic agent. However, the semisynthetic illudin analogue, 6-(hydroxymethyl)acylfulvene (HMAF),[4] shows outstanding activity against breast, colon, lung, pancreas, prostate, and skin cancers and is now in various Phase I, II, and III clinical trials.[5]

Illudin C,[1c] C_2[1d], and C_3[1d] and illudinic acid[1e] have only recently been isolated, and the latter three have been shown to possess antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA).[1d,e] The anticancer activity of these compounds has not been reported, although cytotoxicity in a mammalian cell culture system has been demonstrated.[1e] Although the total synthesis of the illudin S/M type of natural products has been extensively investigated,[6] no synthetic entry to the illudin C variant is presently available. In view of the successful analogue breakthrough in the illudin S/M series, an efficient synthetic entry to the illudin C type of natural products is highly desirable in order to more fully investigate the cytotoxic properties of these compounds and congeners. Herein we describe a flexible, convergent strategy for the preparation of the illudin C class of compounds that features a two-step elaboration of the fully functionalized tricyclic ring system from appropriately substituted cyclopentene and cyclopropane precursors.

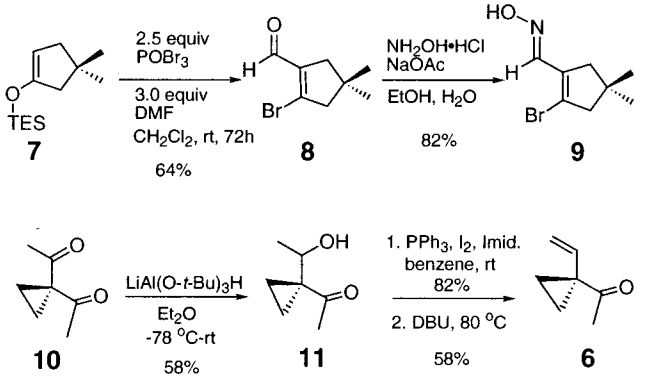
Our retrosynthetic analysis for the synthesis of illudin C (**1**) is outlined in Scheme 1. On the basis of the pioneering investigations of Curran and Kozikowski,[7] it was envisaged that the α-methylene ketone functionality of illudin C could be introduced via dehydration of the corresponding β-hydroxy ketone, in turn available from the hydrogenolysis−hydrolysis reaction of isoxazoline **2**. The conformationally restricted alkenyl nitrile oxide **3** was anticipated to be an excellent substrate for an intramolecular dipolar cycloaddition to furnish isoxazoline **2** and could be generated by the standard protocol, namely, oxidation of oxime **4**. While the obvious route to oxime **4** was from the corresponding aldehyde, this would have necessitated prior protection of the aldehyde moiety in order to effect a planned vinyl anion coupling with cyclopropyl ketone **6**. Instead, we were intrigued by the possibility of employing dianion **5**, prepared by metalation of the corresponding β-halo unsaturated oxime, in a more direct synthesis of oxime **4**. Little in the way of precedent for this transformation could be found in the literature, although the preparation and alkylation of the dilithium derivatives of saturated ketoximes (α-Li, O-Li)[8] offered some encouragement to pursue this especially convergent approach.

Scheme 1



To that end, we considered the preparation of cyclopentenecarboxaldehyde **8** using a Vilsmeier−Haack procedure (Scheme 2). Several examples in the literature suggested that this compound could be obtained from 3,3-dimethylcyclopentan-1-one by regioselective attack of the bromo(dimethylamino)methyl cation on the less encumbered enol (**7**, TES

Scheme 2



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(3) Moreover, the damage produced by illudin S appears to differ from that of other known cytotoxic agents since ERCC2 and ERCC3 (excision repair cross complementing) helicases are required for repair.[2a] These helicases, as opposed to ERCC1, are not upregulated in drug-resistant tumors, which may be the underlying basis for the increased sensitivity of certain MDR cell lines to the illudins.[2a]

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(5) These studies are being undertaken by MGI Pharma. For an extensive compilation of relevant literature references, see: http://www.mgipharma-.com/Products_in_Development/MGI_114/body_mgi_114.html.

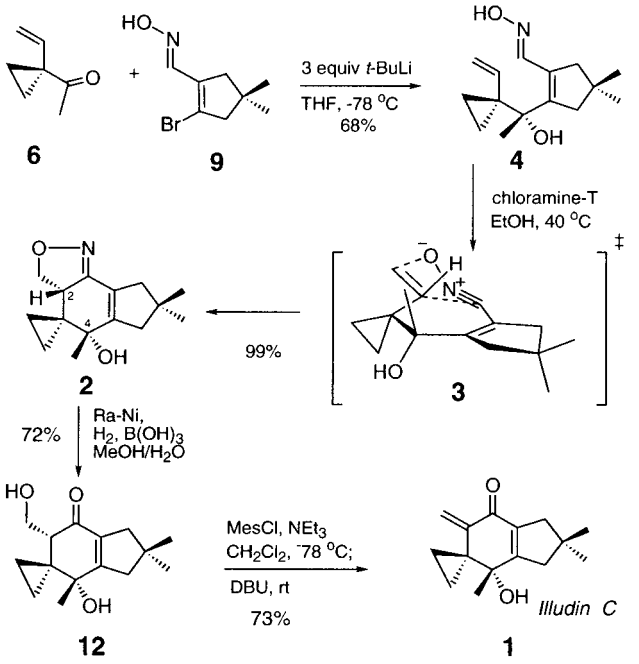
(6) For previous synthetic effort, see: (a) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kawawa, S.; Sakan, F.; Matsumoto, S.; Nishida, S. *J. Am. Chem. Soc*. **1968**, *90*, 3280. (b) Matsumoto, T.; Shirahama, H.; Ichihara, A.; Shin, H.; Kagawa, S.; Sakan, F.; Miyano, K. *Tetrahedron Lett.* **1971**, *12*, 2049. (c) Kigoshi, H.; Imamura, Y.; Mizuta, K.; Niwa, H.; Yamada, K. *J. Am. Chem. Soc*. **1993**, *115*, 3056. (d) Kinder, F. R., Jr.; Bair, D. W. *J. Org. Chem*. **1994**, *59*, 6965. (e) Padwa, A.; Curtis, E. A.; Sandanayaka, V. P. *J. Org. Chem*. **1997**, *62*, 1317. (f) McMorris, T.; Hu, Y.; Yu, J.; Kelner, M. J. *J. Chem. Soc., Chem. Commun*. **1997**, 315. (g) Pirrung, M. C.; Kaliappan, K. P. *Org. Lett*. **2000**, *2*, 353. (h) Brummond, K. M.; Lu, J. L.; Petersen, J. *J. Am. Chem. Soc*. **2000**, *122*, 4915. (i) Armone, A.; Merlini, L.; Nasini, G.; de Pava, O. V.; Zunino, F. *J. Chem. Soc. Perkin Trans. 1* **2001**, 610.

= H).[9] However, a nearly equal mixture of aldehyde **8** and the regioisomeric product (2-bromo-5,5-dimethylcyclopent-1-enecarboxaldehyde, 1.1:1) was obtained using PBr_3/DMF in methylene chloride. Consequently, we turned to the known silyl enol ether **7**,[10] but unfortunately treatment with PBr_3/DMF afforded the same mixture of regioisomers, presumably through initial hydrolysis of the silyl enol ether. To our delight, if $POBr_3$/DMF in methylene chloride was employed, then only the aldehyde **8** regioisomer was formed in 64% yield.[11] Aldehyde **8** was then converted to the *E*-oxime **9** using the standard protocol in 82% yield.

The preparation of the electrophilic component for the pending coupling reaction, ketone **6** (Scheme 2), was more straightforward and was initiated by bisalkylation of 2,4-pentanedione with 1,2-dibromoethane to provide the known cyclopropane **10**.[12] Monoreduction of diketone **10** to keto alcohol **11** could be accomplished with Li(O-*t*-Bu)$_3$AlH (58%) and was accompanied by only minor amounts of the corresponding diol. Although dehydration of the alcohol **11** to the olefin **6** took place upon treatment with the Burgess reagent, this transformation was best performed by initial conversion to the unstable iodide (82%) followed by distillation from neat DBU to afford the volatile ketone **6** in 58% yield.

We were now in the position to examine the two-step merger of the cyclopropane and cyclopentene sectors of illudin C (Scheme 3). Indeed, the dianion **5** could be prepared by addition of *t*-BuLi (3 equiv) at −78 °C to bromo oxime **9**. To minimize self-condensation products, the cyclopropyl ketone **6** was diluted with THF and added slowly via syringe pump (1 h) to the dianion **5** to afford the desired oxime **4** in 68% yield. We were pleased to discover that the final bond of the tricyclic system formed readily upon treatment of the oxime **4** with chloramine-T (EtOH, 40 °C, 6 h)[13] to deliver the isoxazoline **2** as a single diastereomer (99%). The *cis* stereochemical relationship of the C(4) methyl substituent and C(2) hydrogen atom in the resultant tetracycle was assigned using NOE experiments. The diastereoselectivity is a consequence of preferential cycloaddition of the nitrile oxide through conformer **3** wherein the smaller C(4) hydroxyl substituent, vis-a-vis the C(4) methyl substituent, occupies an equatorial position bisecting the cyclopropane ring.

Scheme 3



Transformation of the nitrile oxide−olefin cycloadduct **2** to illudin C (**1**) was uneventful (Scheme 3). Thus, Raney-Ni-catalyzed hydrogenation of the N−O bond followed by in situ hydrolysis of the resulting β-hydroxyimine according to the Curran protocol (H_2O, $B(OH)_3$)[14] furnished the formal aldol adduct **12** in 72% yield. Finally, the one-pot dehydration of the primary alcohol functionality of diol **12** could be accomplished by standard conversion to the mesylate (MesCl, NEt_3) followed by addition of DBU to provide racemic illudin C (**1**, 73%) identical in all respects with published spectra.[1c]

In summary, we have completed the first total synthesis of illudin C in 10 steps and 8.2% overall yield starting from allyl alcohol and isobutyraldehyde.[10] In the course of the synthesis we have demonstrated that silyl enol ethers can be used in regiospecific Vilsmeier−Haack-type reactions, that β-halo unsaturated oximes permit halogen metal exchange, and that an intramolecular nitrile oxide−olefin cycloaddition facilitates an exceptionally concise route to the illudin tricyclic ring system. The preparation of illudin C analogues, as well as the extension of this synthetic sequence to the construction of other ring systems embodied in biologically active natural products, is underway in our laboratories.

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Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) To the best of our knowledge, this is the first example of a regiospecific Vilsmeier−Haack haloformylation of a silyl enol ether. For the chloroformylation of a silyl enol ether derived from a *symmetrical* ketone (cyclohexanone), see: Reddy, D. P.; Tanimoto, S. *Synthesis* **1987**, 575.

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