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Synthesis and structural revision of annuionone A

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Abstract—Annuionones (**1**–**5**), allelopathic agents isolated from *Helianthus annus* (sunflower), were reported to be ionone-type bisnorsesquiterepenes. However, the proposed structures for annuionones A (**1**), B (**2**) and E (**5**) were thought to be incorrect. Thus, we have tentatively proposed a revised structure (**6**) for annuionone A based on careful re-analyses of the reported spectral data. The synthesis of (±)-**6** was accomplished to prove the structure of natural annuionone A as **6**.

In 1998, Macías and his co-workers isolated annuionones A–C (**1**–**3**) from *Helianthus annus* (sunflower), as allelopathic agents.[1] Then the isolation of annuionones D[2] (**4**) and E[3] (**5**) was also reported in 1999 and 2002, respectively. Annuionones A (**1**), B (**2**) and E (**5**) are structurally unique ionone-type bisnorsesquiterepenes with an *exo*-epoxide moiety. The unique structure and bioactivity of annuionones prompted us to synthesize them as a part of our synthetic studies on terpenoids with allelopathic activity.[4]

Before starting our synthetic studies, we found some uncertain points concerning the proposed structures for annuionones A, B and E. The most questionable points are the chemical shift values of H-11 and C-11, for example, $\delta_H = 3.54$ and 3.61, and $\delta_C = 78.3$ (ppm) in annuionone A.[1] Those chemical shift values were thought to be rather low field shifted for usual epoxide-methylene. Thus we carefully re-analyzed the reported spectral data and have reached the conclusion that the correct structure of natural annuionone A might be **6** as illustrated in Figure 1, aside from the absolute configuration. This structure does not conflict with most of the reported data. Based on this speculation, we started a project to synthesize (±)-**6** for clarification of the structure of annuionone A. The synthesis of (±)-**6** was accomplished, and thereby the structure of annuionone A was revised to be not **1** but **6**. Herein, we report the results of our studies.

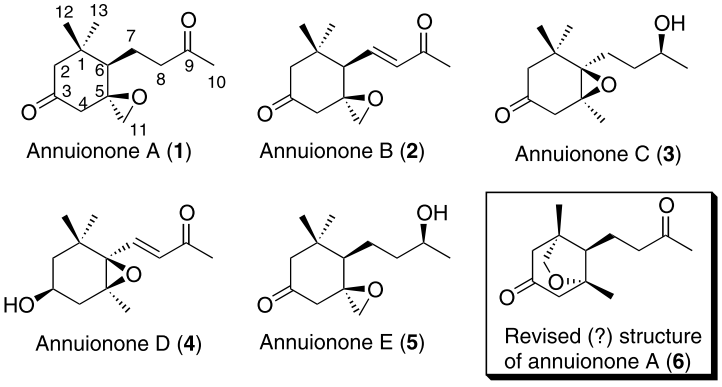

Figure 1. Structures of annuionones.

Keywords: sesquiterpenoids; allelopathic agents; oxy-Michael addition; Wacker oxidation.
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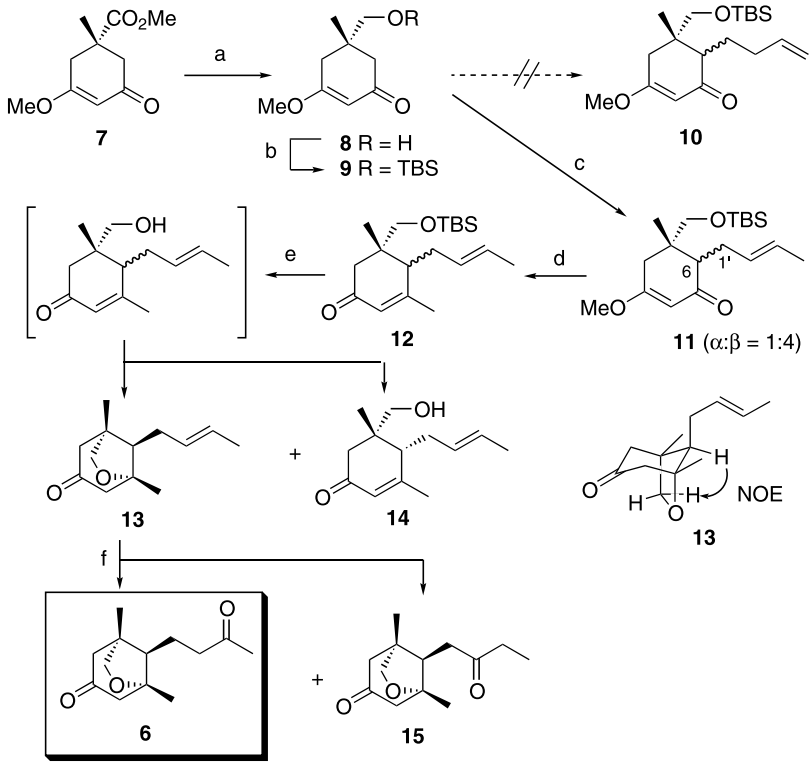

Scheme 1. Synthesis of (±)-**6**. *Reagents and conditions*: (a) LDA, THF; DIBAL, toluene (76%); (b) TBSCl, imidazole, DMF (92%); (c) LDA, THF; crotyl bromide, HMPA (60%); (d) MeLi, Et_2O; sat. aq. NH_4Cl (93%); (e) TBAF, THF (72%); (f) $PdCl_2$, CuCl, O_2, aq. DMF (54% for **6** and 16% for **15**).

Our synthetic route to (±)-**6** is simple as illustrated in Scheme 1. First, the known ketoester **7**[5] was treated with LDA and then DIBAL to give **8** (76%), which was subsequently protected as the TBS ether to furnish **9** (92%). For installation of the 3-oxo-butyl side-chain, we attempted homoallylation of **9**, because a homoallyl group was thought to be convertible into a 3-oxo-butyl group with ease by Wacker oxidation.[6] However, in spite of our efforts, the conversion of **9** into **10** was not successful.[7] Thus, we then turned to crotylation of **9**, which was performed by treatment with LDA and crotyl bromide in the presence of HMPA, furnishing **11** as a diastereomeric mixture (60%). The diastereomeric ratio was estimated to be ca. 4:1 based on ^{1}H NMR analysis. It could be easily deduced that the major diastereomer should be the β-isomer, because the β-face of enolate anion of **9** might be less hindered than the α-face. However, its relative configuration could not be determined by NOE studies, because these two diastereomers were chromatographically inseparable and the signals assigned as 6- and 1′-H were poorly resolved. Therefore, this mixture was used for the next step without further purification. Treatment with MeLi and the following work-up could convert **11** into **12** (93%). After removal of the TBS protecting group, concomitant intramolecular oxy-Michael addition took place to give the desired adduct **13** (72%), leaving the α-isomer (**14**) unaffected. The relative configuration of **13** was confirmed by the observation of NOE as depicted in Scheme 1. Finally, Wacker oxidation[6] of **13** was followed by SiO_2 column chromatography to furnish **6** (54%) and its regioisomer **15** (16%), respectively.[8] The overall yield of **6** was 15% (six steps) based on **7**.

The spectral data of the synthetic (±)-**6**[9] are in good accord with those of the natural annuionone A.[1] Hereby, it is confirmed that the correct structure of the natural annuionone A is not **1** but **6**. Furthermore, judging from the similarity of NMR data, it is also strongly suggested that the structures of the natural annuionone B and E should be **16** and **17**, respectively, as shown in Figure 2. These results and suggestions are completely supported by comprehensive spectroscopical studies of annuionones performed by Macías and his co-workers independently of this work.[10]

In conclusion, we have accomplished the first synthesis of (±)-annuionone A (**6**), which enabled us to clarify the structures of annuionones A, B and E. However, the absolute configurations of annuionones still remain unknown. Thus, for the unambiguous determination of the absolute configurations of annuionones, enantioselective synthesis of annuionones is now under way in our group.

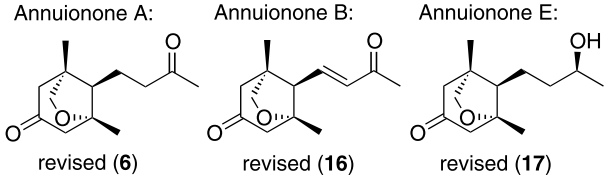

Figure 2. Structural revision of annuionones.

Acknowledgements

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7. The following are the tested reaction conditions for the alkylation of **9** with 4-bromo-1-butene: LDA, THF, HMPA, −78°C to room temp.; KHMDS, 18-crown-6, THF, −78°C to room temp.
8. It was noteworthy that the use of a stoichiometric amount of $PdCl_2$ gave **15** as the major product.
9. Properties of (±)-**6**: colorless needles; mp 44–45°C (from hexane–Et_2O); IR ν_{max} (CCl_4) 1725 (s, C=O), 1710 (C=O) cm^{-1}; EIMS m/z (rel. int.) 224 (3), 181 (2), 167 (18); HREIMS obsd 224.1418 calcd for $C_{13}H_{20}O_3$ 224.1412; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 1.08$ (3H, s), 1.32 (3H, s), 1.61–1.69 (2H, m), 1.78–1.88 (1H, m), 2.19 (3H, s), 2.23 (1H, d, $J = 17.7$ Hz), 2.33–2.42 (3H, m), 2.66 (2H, t-like, $J = 6.6$ Hz), 3.57 (1H, dd, $J = 2.7$, 7.8, Hz), 3.64 (1H, d, $J = 7.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 18.5$, 20.7, 24.8, 30.0, 42.5, 43.4, 48.5, 49.3, 53.0, 78.2, 83.3, 207.4, 208.9.
   NMR data of natural annuionone A[1]: ^1H NMR (400 MHz, $CDCl_3$) $\delta = 1.05$ (3H, s), 1.29 (3H, s), 1.61 (2H, m), 1.80 (1H, dddd, $J = 8.0$, 8.0, 8.0, 15.9 Hz), 2.16 (3H, s), 2.22 (1H, d, $J = 17.7$ Hz), 2.34 (1H, d, $J = 17.6$ Hz), 2.37 (1H, dd, $J = 2.9$, 17.7 Hz), 2.39 (1H, d, $J = 17.6$ Hz), 2.63 (1H, ddd, $J = 8.0$, 8.0, 8.0 Hz), 2.63 (1H, m), 3.54 (1H, dd, $J = 2.9$, 7.9 Hz), 3.61 (1H, d, $J = 7.9$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 18.7$, 20.8, 24.9, 30.0, 42.6, 43.4, 48.6, 49.4, 53.1, 78.3, 83.4, 207.2, 208.7.
10. Macías and his co-workers have already reached the same conclusion independently: Macías, F. A.; López, A.; Varela, R. M.; Torres, A.; Molinillo, J. M. G. *Phytochemistry*, **2003**, submitted.