A New Access to Mori's Intermediate for the Practical Synthesis of (–)-Periplanone-B

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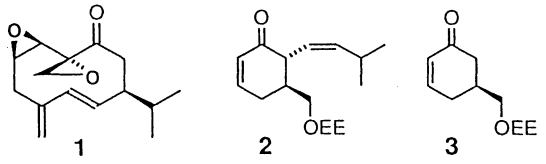
Mori's key intermediate **2** for the large-scale synthesis of (–)-periplanone-B has been prepared from β-keto prenyl ester **8** by exploiting the new three-step sequence of α-alkynylation with alkynyllead(IV) triacetate, semihydrogenation, and palladium-catalyzed deallyloxycarbonylation with HCO_2HNEt_3, and subsequent isomerization induced by $NaOCH_3$.

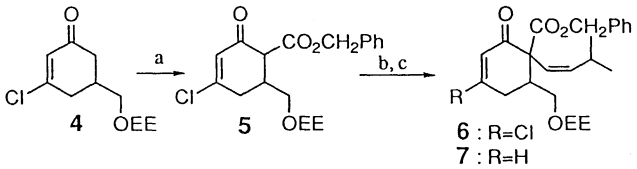
The utility of α-alkenyl ketones as synthetic intermediates for a wide range of transformations, *inter alia*, ring expansion reactions *via* Cope, anionic oxy-Cope, or Cope-Claisen rearrangement, has spurred development of expeditious methods for the regiocontrolled introduction of a stereo-defined alkenyl group α to the carbonyl of unsymmetrical ketones.[1] In this context, we recently devised controlled methods for the synthesis of α-(*E*)- and α-(*Z*)-1-alkenyl ketones from β-keto benzyl esters by exploiting the sequence of α-alkenylation or α-alkynylation with organolead(IV) triacetates, semihydrogenation (only for (*Z*)-1-alkenyl series), and reductive removal of a benzyloxycarbonyl group with W-2 Raney nickel in the presence of triethylamine.[2,3] The effectiveness of the protocol for the elaboration of α-(*E*)-1-alkenyl ketones was demonstrated well by our convergent synthesis of (+)-isocarbacyclin.[2,4] Thus, our efforts were centered on the application of the (*Z*)-counterpart to the synthetically useful intermediates for biologically active natural products. We now wish to report the synthetic approach to Mori's intermediate[5] for the total synthesis of (–)-periplanone-B (**1**), a sex pheromone component of the American cockroach (*Periplaneta americana*), in which a new method for α-(Z)-1-alkenyl ketone synthesis from β-keto prenyl ester has been developed.



1 2 3

Several groups accomplished the total synthesis of periplanone-B by devising innovative strategies and tactics.[6] Of these, Kuwahara and Mori[5] recently succeeded in a highly efficient and practical synthesis of (–)-**1** *via* vinylation of α-(*Z*)-alkenyl cyclohexenone **2** and subsequent anionic oxy-Cope rearrangement, in which the most crucial point was the preparation of **2**, the optically active and (*Z*)-isomer of Still's intermediate.[6a] Although they felicitously prepared the key intermediate **2** by aldol reaction of the ketone **3** with α-phenylselenoisovaleraldehyde followed by mesylation and subsequent elimination,[1b,d] the strictly controlled reaction condition was required to decompose the undesired diastereomer leading to the (*E*)-isomer formed in the aldol reaction. Taken it into consideration, our interest was focused on the feasibility of our method for the preparation of **2**.

At the outset, a racemic approach was explored (Scheme 1). In the synthesis of α-alkenyl cyclic enone such as **2**, the enone moiety without any substituent on a double bond should be protected because of saturation of a double bond concurrent with debenzyloxycarbonylation by W-2 Raney nickel.[2] Thus, we chose the β-chloroenone **4**[7] as a substrate, which was converted into the β-keto benzyl ester **5** by Mander's method using benzyl cyanoformate.[8] Although the improved Pinhey's α-alkynylation of **5** with the alkynyllead(IV) triacetate, generated *in situ* from 3-methyl-1-butynyllithium and lead tetraacetate,[3] proceeded in high yield, the product **6** was found to be accompanied by serious amounts of dechlorinated enone **7** at the stage of Lindlar reduction. This problem led us to abandon the original scenario and to develop a more versatile method.



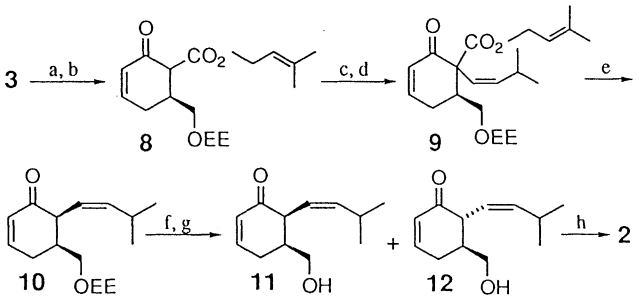
4 5 6 : R=Cl 7 : R=H

Reagents and conditions: (a) $(Me_3Si)_2NLi$ (1.2 equiv.), THF, –78 °C, 0.5 h; $NCCO_2CH_2Ph$ (1.2 equiv.), HMPA, –78 °C, 1 h, 83%. (b) 3-methyl-1-butynyllithium (2.1 equiv.), $Pb(OAc)_4$ (2.0 equiv.), CH_2Cl_2-THF (5:1), 23 °C, 0.5 h. (c) H_2, Lindlar cat., benzene, 23 °C, 1 h, 42% of **6** and 23% of **7** from **5**.

Scheme 1.

Toward this end, it occurred to us that β-keto allyl ester might be the substrate of choice, since palladium-catalyzed deallyloxycarbonylation reaction by Tsuji and his coworkers[9] was demonstrated to proceed chemoselectively under mild and nearly neutral conditions. In model studies, α-hexynylation of allyl 2-oxo-3-cyclohexenecarboxylate was effected in 85% yield, but a C-C double bond in the ester moiety was found to be easily hydrogenated by Lindlar reduction. After variations of substituents on allylic alcohols, 3-methyl-2-butenyl (prenyl) ester proved to be the best choice for allowing selective semihydrogenation as well as high-yield alkynylation. Eventually it was found that subsequent deallyloxycarbonylation using $Pd(OAc)_2$/PPh_3-HCO_2HNEt_3[9] proceeded smoothly at 40 °C to give 6-[(*Z*)-1-hexenyl]-2-cyclohexenone in 68% overall yield, without any evidence of double bond migration.

With a facile access to α-(*Z*)-alkenyl cyclic enones developed,[10] we then applied this protocol to the preparation of **2** in an optically active form (Scheme 2). β-Keto prenyl ester **8** was prepared from optically pure cyclohexenone **3**[5] by *C*-methoxycarbonylation followed by transesterification with prenyl alcohol. The three-step sequence of α-alkynylation of **8**, semihydrogenation, and palladium-catalyzed deallyloxycarbonylation proceeded uneventfully to give the α-(*Z*)-alkenyl enone **10**, $[\alpha]_D^{24}$ –96.8°(*c* 3.17, hexane), in 63% yield. The specific

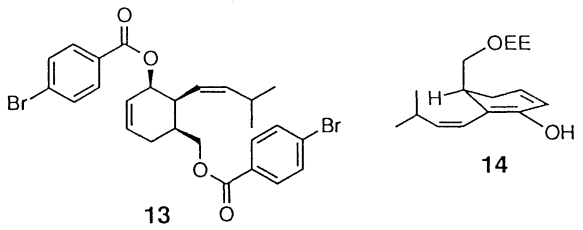


Reagents and conditions: (a) $(Me_3Si)_2NLi$ (1.2 equiv.), THF, −78 °C, 0.5 h; $NCCO_2CH_3$ (1.2 equiv.), HMPA, −78 °C, 1 h. (b) 3-methyl-2-buten-1-ol (3 equiv.), 180 °C, 1 h, 74% from **3**. (c) 3-methyl-1-butynyllithium (2.1 equiv.), $Pb(OAc)_4$ (2.0 equiv), CH_2Cl_2-THF (5:1), 23 °C, 0.5 h. (d) H_2, Lindlar cat., benzene, 23 °C, 1 h, 73% from **8**. (e) $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), HCO_2HNEt_3 (20 equiv.), THF, 40 °C, 1 h, 86%. (f) $NaOCH_3$ (5 equiv.), MeOH, 0 °C, 0.5 h. (g) 10% HCl-THF (1:10), 50 °C, 1 h, 30% of **11** and 55% of **12** from **10**. (h) ethyl vinyl ether, PPTS, CH_2Cl_2, 23 °C, 16 h, 94%.

Scheme 2.

rotation of **10** was quite different from that reported with **2**.[5b] 400 MHz ^1H NMR spectrum of **10** demonstrated (*Z*)-geometry in the side-chain without any signal for the (*E*)-isomer, but could not define the stereochemistries at C-5 and C-6 due to the presence of the asymmetric acetal carbon of the protecting group. On the other hand, ^1H NMR spectrum of the deprotected alcohol **11** suggested that the C-5/C-6 relationship might be *cis* as inferred by 4.3 Hz coupling constant between their protons. To confirm the stereochemistry unambiguously, **10** was converted into the bis-(*p*-bromobenzoate) **13**,[11] mp 148-148.5 °C (CH_3CN), the single-crystal X-ray structural analysis of which revealed that **10** was thermodynamically less stable 5,6-*cis*-disubstituted cyclohexenone. The unexpected stereochemical outcome may be interpreted by considering that kinetic proton transfer from the enol intermediate **14** to give the ketone occurs exclusively from the less hindered α-face, in which the side-chain at C-5 shields the β-face effectively due to a planarity of a cyclohexadiene ring of **14**.

The stage was then set for an examination of the isomerization of **10** to **2**. Of the bases such as Et_3N, metal alkoxides, and lithium diisopropylamide screened, $NaOCH_3$ in MeOH proved to be the best choice. Although the 1,4-addition of MeOH to the enone moiety of **10** was observed, the elimination of MeOH occurred during deprotection of the ethoxyethyl group with hydrochloric acid in THF. It should be noted that little migration



of a double bond in the side-chain was observed under these conditions. The 35:65 mixture of the *cis*-isomer **11** and the *trans*-isomer **12** thus obtained was easily separated by column chromatography on silica gel.[12] The hydroxyl group of the desired *trans*-isomer **12** ($J_{5,6}$=10.7 Hz) was again protected as the ethoxyethyl ether **2**, $[\alpha]_D^{22}$ +99.1°(*c* 2.72, hexane)[lit.[5b] $[\alpha]_D^{20}$ +90.7°(*c* 3.00, hexane)]. The spectroscopic data including specific rotation were completely identical with those of Mori's intermediate.

In conclusion, we have accomplished a new access to Mori's pivotal intermediate **2** for the practical synthesis of (−)-periplanone-B by devising an expeditious method for α-(*Z*)-alkenyl cyclic enone synthesis.

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7 β-Chloroenone **4** was prepared from 3,4,5-trimethoxybenzoic acid in 7 steps; (1) Na, liq.NH_3, −78 °C; (2) $LiAlH_4$, ether, 0 °C; (3) Ac_2O, pyridine, 23 °C; (4) CF_3CO_2H, 0 °C; (5) $(COCl)_2$, $CHCl_3$, 23 °C; (6) K_2CO_3, MeOH, −20 °C; (7) ethyl vinyl ether, *p*-TsOH, ether, 23 °C.

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10 Full details on the scope and potency of the preparation of α-(*Z*)-1-alkenyl ketones from β-keto prenyl esters will be reported in due course.

11 The three-step conversion was performed as follows. (1) $NaBH_4$-$CeCl_3$, MeOH, 0 °C. (2) 10% HCl-THF (1:10), 23 °C, 90% (two steps). (3) *p*-bromobenzoyl chloride, pyridine, 23 °C, 92%.

12 TLC R_f values (3:1 ether/hexane): **11**, 0.14; **12**, 0.19.