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A new preparation of 2,5-dihydro-1-benzoxepins using Mitsunobu cyclization, and the synthesis of natural radulanins

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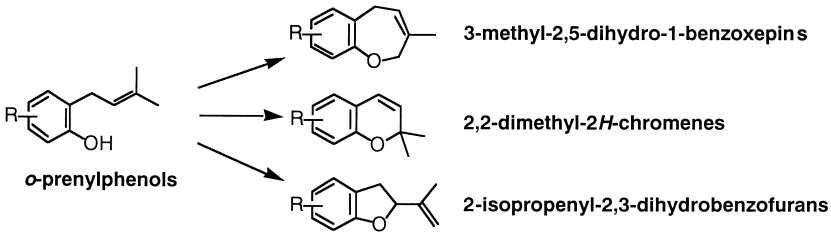
Abstract

Mitsunobu cyclization of *o*-[4-hydroxy-3-methyl-2(*Z*)-butenyl]phenol **2a** effected selective seven-membered cyclization to give 3-methyl-2,5-dihydro-1-benoxepin **1a**. Using this procedure, natural radulanin A and radulanin A methyl ether were synthesized effectively.

Many compounds having a 3-methyl-2,5-dihydro-1-benzoxepin structure (**1a**) have been isolated from various plants.[1] Similar to 2-isopropenyl- 2,3-dihydrobenzofurans and 2,2-dimethyl-2*H*-chromenes, they might be biogenetically derived from *o*-prenylphenols.



In our studies on naturally occurring 2-isopropenyl-2,3-dihydrobenzofurans and 2,2-dimethyl-2*H*-chromenes, we found some seven-membered cyclizations (especially in 2,4,6-trihydroxyacetophenone or 2,6-dihydroxyacetophenone)[2] and some photo-ring expansions (especially in 6-methoxy-2,2-dimethyl-2*H*-chromene or 5-methoxy-2-isopropenyl-2,3-dihydrobenzofuran).[3] But there was no general method for the preparation of **1a** until the recent ring-closing metathesis.[4] In this paper, a new method using Mitsunobu cyclization is described.

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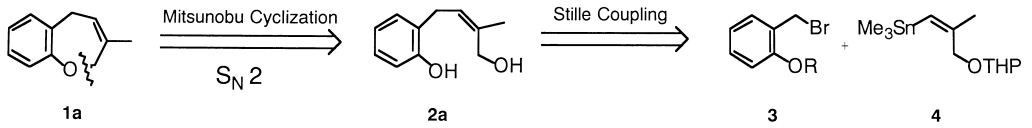
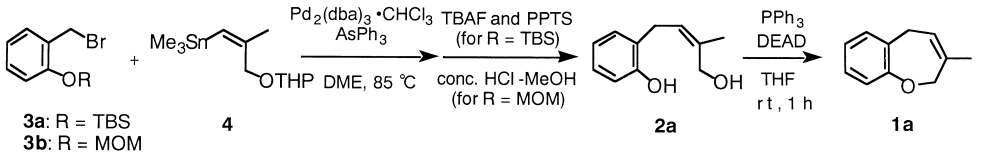
In our new strategy for **1a** (Scheme 1), **1a** might be prepared from diol **2a**, and **2a** might be prepared by Stille coupling of benzyl bromide **3** with stannane **4**. This cyclization of *Z*-methyl-oxidized *o*-prenylphenols **2a** is a biomimetic procedure, but there are two possibilities: desired seven-membered cyclization via S_N2 to give **1a**, and five-membered cyclization via S_N2' to give 2-isopropenyl-2,3-dihydrobenzofuran. For a selective seven-membered cyclization, diol **2a** was subjected to Mitsunobu cyclization known as a typical S_N2 reaction.[5]



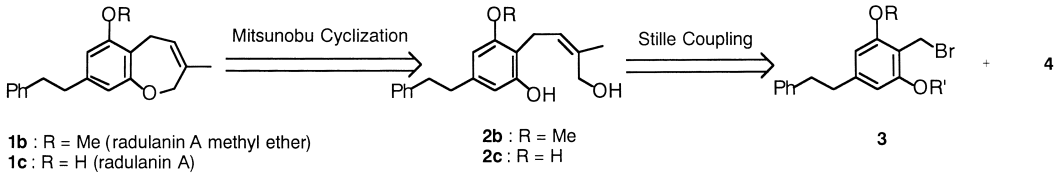
Scheme 1.

As the substrates of the Stille coupling, (TBS-oxy)benzyl bromide **3a** was prepared from *o*-cresol in two steps (90%): TBS protection with TBSCl, and bromination with NBS, and (MOM-oxy)-benzyl bromide **3b** was prepared from salicylaldehyde in three steps (83%): MOM protection with MOMCl, LiAlH4 reduction, and bromination with PBr_3. The stannane **4** as the Stille coupling partner was prepared according to the reported method.[6] Diol **2a** was obtained from **3a** in three steps (41%): Pd(0)-catalyzed Stille coupling of **3a**[6,7] with **4** (crude 73%), deprotection of TBS with TBAF, and deprotection of THP with PPTS (Scheme 2). Diol **2a** was also prepared from **3b** in two steps (67%): Pd(0)-catalyzed Stille coupling of **3b** with **4** (crude 97%) and deprotection with conc. HCl.



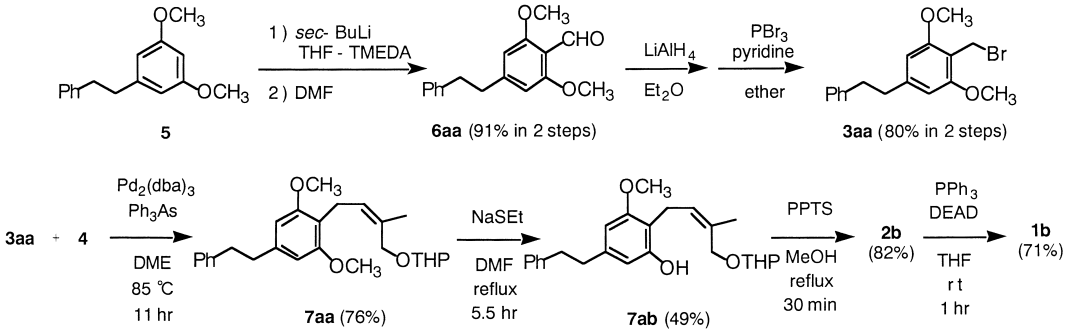
Scheme 2.

Mitsunobu cyclization of diol **2a** by treating with triphenylphosphine and diethyl azodicarboxylate in dry THF at room temperature for 1 h gave 3-methyl-2,5-dihydro-1-benzoxepin **1a** in 87% yield. In this cyclization, only the seven-membered cyclization via S_N2 was observed, and none of the five-membered cyclizations via S_N2' was observed. Thus, Mitsunobu cyclization of (*Z*)-diol might be effective for the preparation of some seven-membered 3-methyl-2,5-dihydro-1-benzoxepins, and this procedure was applied to the synthesis of radulanin A (**1c**) and its methyl ether (**1b**) (Scheme 3), isolated from the Radula species by Asakawa et al.[8]

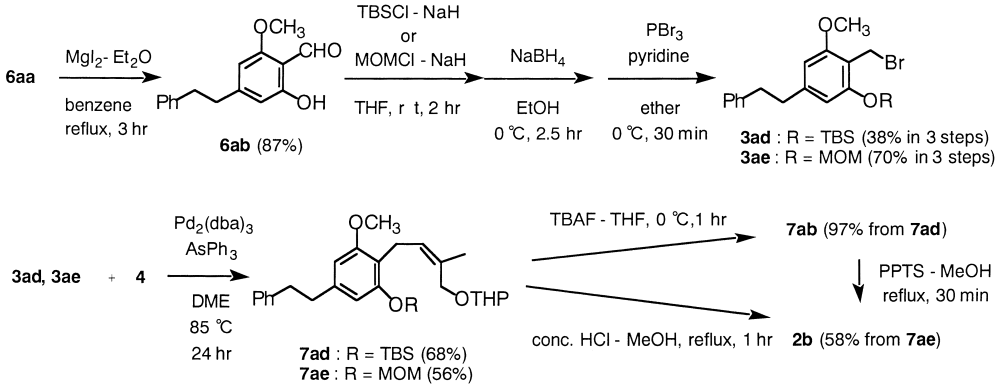


Scheme 3.

Dimethoxybenzyl bromide **3aa** was prepared from 1,3-dimethoxy-5-(2-phenylethyl)benzene (**5**) in four steps: formylation with *sec*-BuLi and DMF to **6aa** (91%), LiAlH4 reduction (86%), and bromination with PBr_3 (93%). Stille coupling of **3aa** with stannane **4** gave **7aa** in 76% (Scheme 4). Demethylation of **7aa** with sodium ethylthiolate gave mono-demethylated **7ab** (49%), which was readily deprotected to diol **2b** with PPTS (82%). Diol **2b** was also obtained from methoxysalicylaldehyde **6ab**, readily prepared by demethylation of **6aa** with magnesium iodide etherate in 87% yield (Scheme 5). Methoxysalicylaldehyde **6ab** was converted to methoxy-(TBS-oxy)benzyl bromide **3ad** or methoxy(MOM-oxy)benzyl bromide **3ae** in three steps: TBS or MOM protection, $NaBH_4$ reduction, and bromination with PBr_3. Stille coupling of benzyl bromides **3ad** and **3ae** gave **7ad** (68%) and **7ae** (56%), which were readily deprotected to diol **2b**: two-steps deprotection of **7ad** with TBAF to **7ab** (97%) and followed with PPTS to **2b** (82%), one-step deprotection of **7ae** with conc. HCl to **2b** (58%). Mitsunobu cyclization of diol **2b**, thus obtained, caused effective seven-membered cyclization to give 6-methoxy-8-(2-phenylethyl)-2,5-dihydro-1-benzoxepin (radulanin A methyl ether) **1b** in 71% yield.



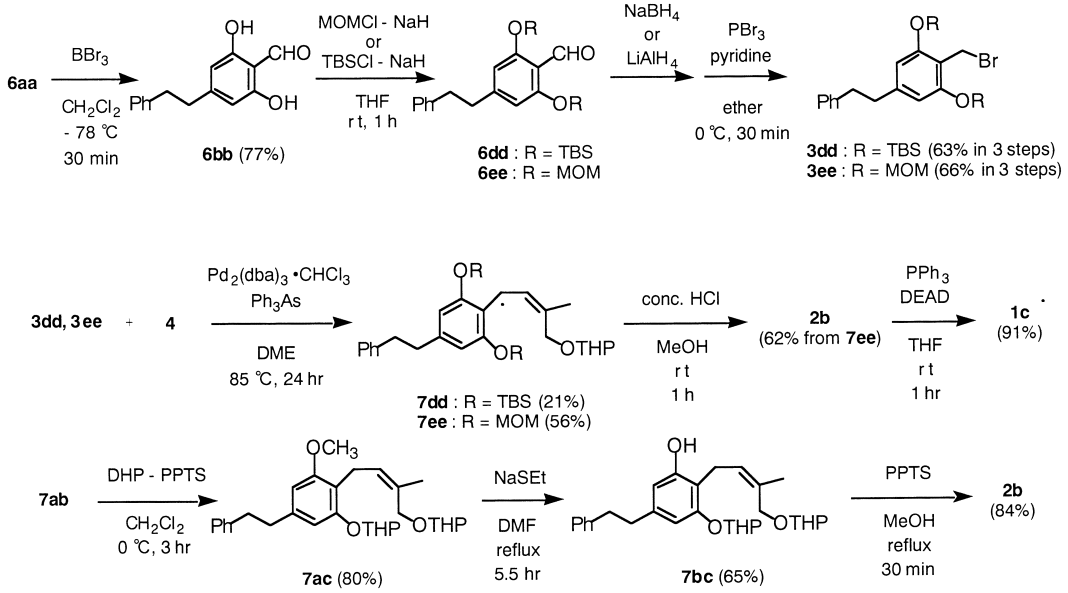
Scheme 4.



Scheme 5.

Demethylation of dimethoxybenzaldehyde **6aa** with boron tribromide effectively gave dihydroxybenzaldehyde **6bb** (Scheme 6). Bis(MOM-oxy)benzyl bromide **3ee** was prepared from **6bb** in three steps (66%): MOM protection with MOMCl, $LiAlH_4$ reduction, and bromination with PBr_3. Stille coupling of **3ee** with **4** also gave **7ee** in 56%, and **7ee** was readily deprotected by treating with conc. HCl to give **2c** in 62% yield. Bis(TBS-oxy)benzyl bromide **3dd** was also prepared from

6bb in three steps (63%): TBS protection with TBSCl, $NaBH_4$ reduction, and bromination with PBr_3, but Stille coupling of **3dd** with **4** showed a lower yield (21%). Triol **2c** was also obtained from **7ab** in three steps, THP protection with DHP-PPTS (80%) to give **7ac**, re-demethylation with NaSEt to **7bc** (65%), and THP deprotection with PPTS (84%). Mitsunobu cyclization of triol **2c**, thus obtained, also caused effective seven-membered cyclization to give 8-(2-phenylethyl)-2,5-dihydro-1-benzoxepin-6-ol (radulanin A) **1c** in 91% yield.



Scheme 6.

The ^1H NMR data of the synthetic **1b** and **1c**, thus obtained, corresponded well to the data of natural radulanin A and radulanin A methyl ether.[8]

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