Hypervalent Iodine Reagents

DOI: 10.1002/ange.200501686

Domino Reaction of 2,3-Epoxy-1-alcohols and PIFA in the Presence of H_2O and the Concise Synthesis of (+)-Tanikolide**

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The domino reaction can perform several reactions in a single operation and is a very powerful tool to synthesize organic compounds. The development of new and efficient domino

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[**] This work was supported by Grants-in Aid for Scientific Research (S) from the Ministry of Education, Culture, Sports, Science, and Technology (Japan). PIFA = phenyliodine(III) bis(trifluoroacetate).

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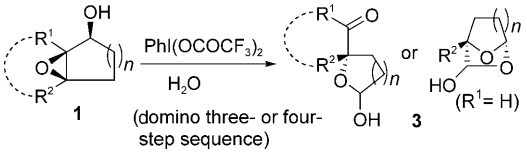
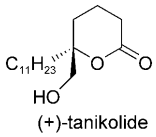
reactions is, therefore, a very attractive subject in the field of synthetic organic chemistry.[1] We present herein an efficient domino reaction in which a three- or four-step sequence occurs in a single operation. Thus, the reaction of 2,3-epoxy-1-alcohols[2] with hypervalent iodine(III) reagents[3] in the presence of H_2O allowed the efficient domino three- or four-step sequence to produce lactols **3** in a single operation (Scheme 1). The reaction was applied to the concise synthesis of (+)-tanikolide.



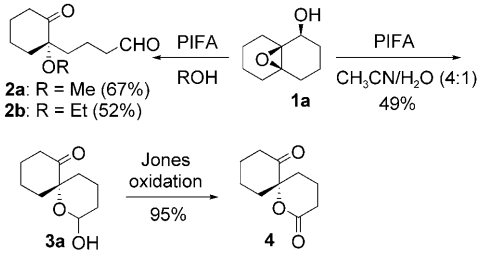
Scheme 1. Domino reaction of 2,3-epoxy-1-alcohols with PIFA in the presence of H_2O.



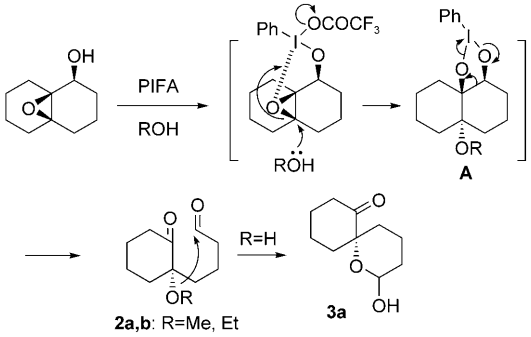
The reaction of bicyclic 2,3-epoxy alcohol **1a** with phenyliodine(III) bis(trifluoroacetate) (PIFA) was examined in the presence of an oxygen-containing nucleophile, an alcohol, or H_2O (when an alcohol was used, it was also employed as the solvent; Scheme 2). A mixture of **1a** (1.0 mmol) in ROH or H_2O/CH_3CN (1:4; 10 mL) was treated with PIFA (1.0 mmol) at 0 °C–RT, with the reaction proceeding smoothly for both nucleophiles. Methoxy keto aldehyde **2a** was obtained in moderate yield from the use of MeOH as the nucleophile, and a similar product **2b** was obtained from EtOH. On the other hand, the lactol **3a** (a mixture of diastereoisomers differing at the acetal position) was obtained from using H_2O. Compound **3a** was converted into the keto lactone **4** by the Jones oxidation.

The formation of **2a**,**b** and **3a** from **1a** is rationalized as follows: first, nucleophilic attack of ROH (R = Me, Et, H) on the oxirane ring gave the alkoxy or hydroxy intermediate **A**, whose C–C bond between the two hydroxy groups was cleaved to give keto aldehyde **2a**,**b** in good yield.[4] When H_2O was used as the nucleophile, a further lactol formation occurred to afford **3a** (Scheme 3).

The generality of the lactol formation was examined next by using various types of epoxy alcohols (Table 1). The bicyclic epoxy alcohols **1a**,**b** gave bicyclic keto lactols **3a**,**b** in fairly good yields (entries 1 and 2). The bicyclic dioxaspiro lactols **3c–i** were obtained in good yields from the monocyclic trisubstituted epoxy alcohols **1c–i**.[5] The formation of **3c–i** is rationalized as a further lactol formation between the hemiacetal hydroxy function and the aldehyde (Scheme 4). No further lactol formation was observed in the keto lactols **3a**,**b**, possibly because access to the ketone moieties is more hindered than to the aldehyde moieties.



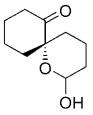
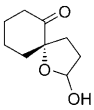
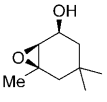
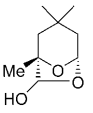
Scheme 2. PIFA treatment of **1a** in the presence of an oxygen-containing nucleophile.

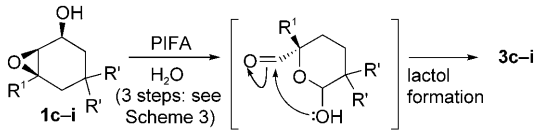


Scheme 3. Plausible reaction mechanism for the formation of **2** and **3**.

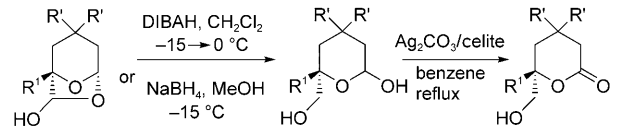
The bicyclic keto lactols were converted into the corresponding lactones in two steps. Thus, the reduction of **3e**,**h** with diisobutylaluminum hydride (DIBAH) or the reduction of **3i** of with $NaBH_4$ gave dihydroxy lactols **4e**,**h**,**i**, which were oxidized using Ag_2CO_3/celite[6] to afford the desired lactones **5e**,**h**,**i** in fairly good yields (Scheme 5).

Table 1: Reaction of various 2,3-epoxy alcohols with PIFA in the presence of H_2O.

Entry	Substrate		Product		Yield [%]
1		**1a**		**3a**	49
2		**1b**		**3b**	66
3		**1c** (R^1 = Me)		**3c** (R^1 = Me)	62
4		**1d** (R^1 = Et)		**3d** (R^1 = Et)	74
5		**1e** (R^1 = *n*-$C_{11}H_{23}$)		**3e** (R^1 = *n*-$C_{11}H_{23}$)	72
6		**1f** (R^1 = CH_2CHMe_2)		**3f** (R^1 = CH_2CHMe_2)	67
7		**1g** (R^1 = CH_2Ph)		**3g** (R^1 = CH_2Ph)	72
8		**1h** (R^1 = Ph)		**3h** (R^1 = Ph)	53
9		**1i**		**3i**	65



Scheme 4. Plausible reaction mechanism for the formation of bicyclic lactols **3c–i**.

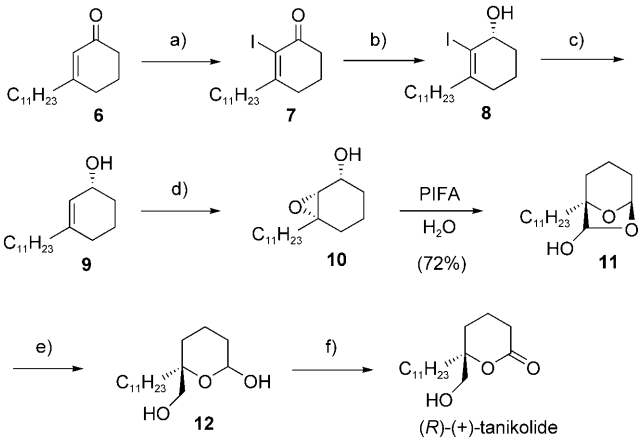


3e: $R^1 = n\text{-}C_{11}H_{23}$, R' = H
3h: R^1 = Ph, R' = H
3i: $R^1 = CH_3$, R' = CH_3

4e, **4h**, **4i**

5e (57% over 2 steps)
5h (57% over 2 steps)
5i (98% over 2 steps)

Scheme 5. Conversion of bicyclic lactols into lactones.



Scheme 6. Concise asymmetric synthesis of (*R*)-(+)-tanikolide. a) I_2, trimethylsilyl azide, pyridine, 0°C→RT (80%); b) (*S*)-5,5-diphenyl-2-methyl-3,4-propan-1,3,2-oxazaborolidine, BH_3Me_2S, THF, 0°C (93%); c) Et_3B, nBu_3SnH, toluene, 0°C–RT (84%); d) *t*BuOOH, [VO(acac)$_2$] (acac = acetylacetonate), benzene, 0°C→RT (96%); e) DIBAH, CH_2Cl_2, −15→0°C; f) $AgCO_3$/celite, benzene, reflux (57% over 2 steps).

With the general transformation of epoxy alcohols to lactols and lactones now available, the application of this method to the concise asymmetric synthesis of (+)-tanikolide was examined next. (+)-Tanikolide is a γ-lactone metabolite of the marine cyanobacterium *Lyngbya majuscula*, which was collected on Tanikeli Island, Madagascar, in 1999 and shows antifungal activity.[7] The enone **6**[8] was converted into the α-iodo enone **7** in 80% yield by using the procedure developed by Sha and Huang.[9] The asymmetric reduction of **7** with the Corey reagent[10] afforded *R*-allyl alcohol **8** in 93% yield with 98% *ee* (optical purity was 98% *ee*, as determined by HPLC analysis of **9** (chiralcel OD and elution with hexane/*i*PrOH (99:1)). The radical reduction[11] of **8** afforded **9** in 84% yield. The stereoselective epoxidation[12] of **9** gave the *cis*-epoxy alcohol **10**. The treatment of **10** with PIFA gave the lactol **11** in 72% yield. Reduction of **11** with DIBAH gave the hydroxy lactol **12**. Chemoselective oxidation of the lactol hydroxy function with Ag_2CO_3/celite[6] afforded (+)-tanikolide in 57% yield over two steps (Scheme 6). ^{1}H NMR spectroscopic analysis (500 MHz) of the corresponding (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid ester of (+)-tanikolide[13] determined the *ee* value as 98%. Although several synthetic studies of (+)-tanikolide have already been reported,[14] our synthesis provides an alternative approach with few steps and high optical purity.

In conclusion, we have developed a novel transformation of 2,3-epoxy-1-alcohols into lactols in a single operation. The lactone functionality is present in a large variety of biologically active compounds and natural products. As domino reactions can reduce the number of operations in the synthesis of organic compounds, this method opens up a new approach to obtaining optically active lactone compounds and will be very useful in the field of synthetic organic chemistry.

Experimental Section

General procedure for lactol formation (conversion of **10** into **11**): PIFA (281.3 mg, 0.65 mmol) was added to a stirred solution of **10** (175.6 mg, 0.65 mmol) in H_2O/CH_3CN (1:4 (v/v), 6.5 mL) at 0°C. The reaction mixture was allowed to warm to room temperature and then stirred for 12 h. A saturated aqueous $Na_2S_2O_3$ solution was added to a reaction mixture, and the resulting mixture was extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by column chromatography on SiO_2 using hexane/EtOAc (5:1) as the eluant to give **11** as a single isomer (134.0 mg, 0.47 mmol, 72% yield).

11: colorless crystals; m.p. 45°C; IR (KBr): $\tilde{\nu} = 3360\ cm^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (3H, t, $J = 6.6$ Hz), 1.26 (20H, m), 1.51–1.72 (6H, m), 3.27 (1H, brs), 5.17 (1H, s), 5.67 ppm (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 14.0$, 15.8, 22.6, 23.8, 29.1, 29.2, 29.3, 29.5 (2C), 29.6 (2C), 30.2, 31.8, 34.0, 83.9, 97.1, 102.2 ppm; $[\alpha]_D^{26} = +54.2$ ($c = 0.54$, $CHCl_3$); elemental analysis (%) for $C_{17}H_{23}O_3$: C 71.79, H 11.34; found: C 71.58, H 11.09.

Received: May 17, 2005
Published online: August 11, 2005

Keywords: domino reactions · epoxy alcohols · hypervalent iodine · natural products · oxygen heterocycles

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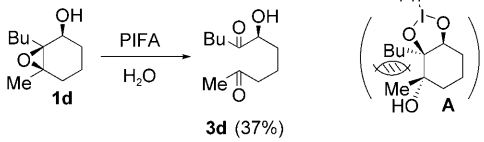

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