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NUCLEOPHILIC PHOSPHINE–CATALYZED IODOCYCLIZATION OF ISOPRENOIDS BEARING AN OXYGEN TERMINAL GROUP

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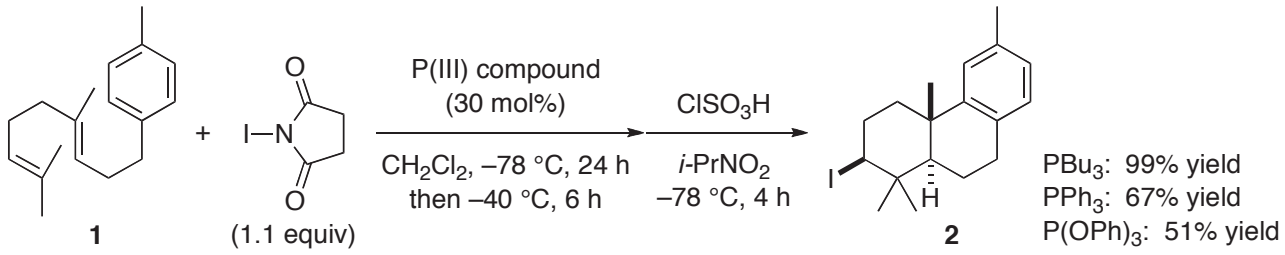
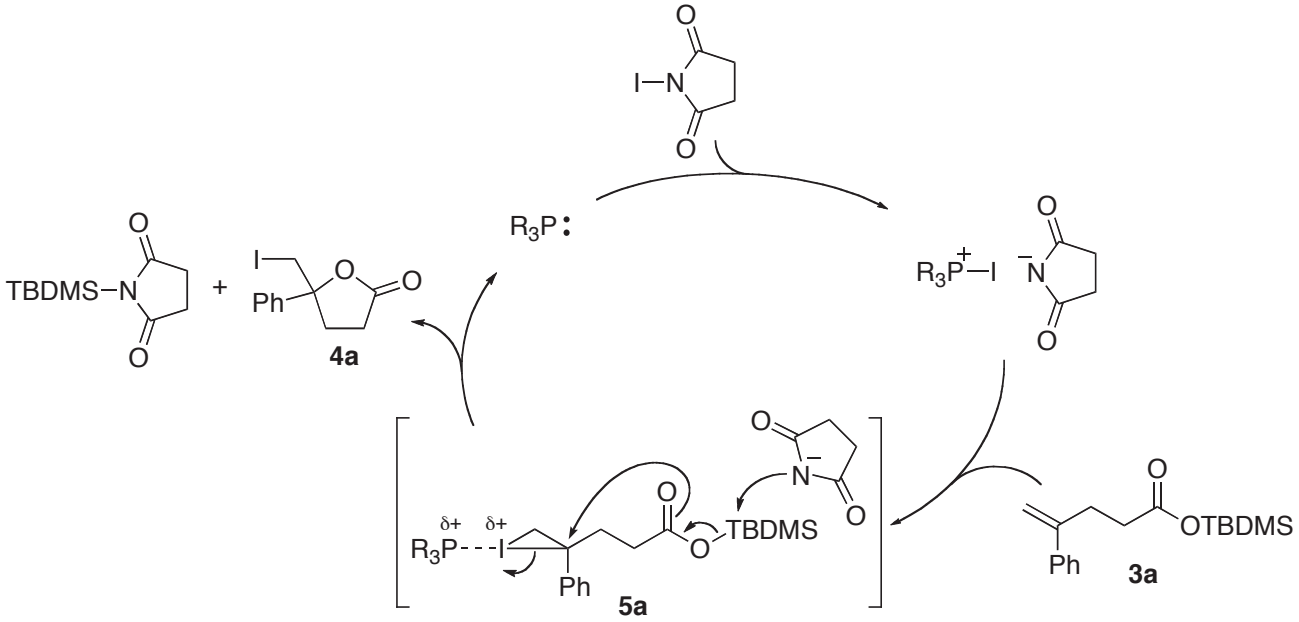
Abstract – The nucleophilic phosphine-catalyzed diastereoselective iodocyclization of linear isoprenoids bearing an oxygen terminal group was investigated. TBDMS ether of homogeraniol and TBDMS ester of homogeranic acid were successfully converted to the corresponding iodopolycyclic products in the presence of a catalytic amount of triphenylphosphine with complete diastereoselectivity.

Diastereoselective halocyclizations induced by the electrophilic addition of a halonium ion to an unactivated alkene are powerful tools in organic synthesis.[1,2] Since these halocyclizations are still conducted under harsh reaction conditions with more than stoichiometric amounts of reagents, the development of effective catalysts that can promote halocyclizations under mild conditions is in high demand. In this context, we recently developed a catalytic diastereoselective iodocyclization of isoprenoids bearing an aryl terminal group.[3] Catalytic amounts of nucleophilic phosphorous(III) compounds activate *N*-iodosuccinimide (NIS) and react with the terminal carbon-carbon double bond of 4-homogeranyltoluene (**1**), which induces diastereoselective cyclization to give **2** in excellent yield (Scheme 1).[4] Highly nucleophilic phosphorous(III) compounds such as tributylphosphine (PBu_3) show good catalytic activities in CH_2Cl_2. During the course of our study, we found that the reactivity of nucleophilic phosphine-catalyzed iodocyclization significantly depended on the structure and nucleophilicity of the terminal functional group. We report here the nucleophilic phosphine-catalyzed iodocyclization of isoprenoids bearing an oxygen terminal group.



1 **2**

Scheme 1. Nucleophilic phosphine-catalyzed iodocyclization of an isoprenoid (previous work)



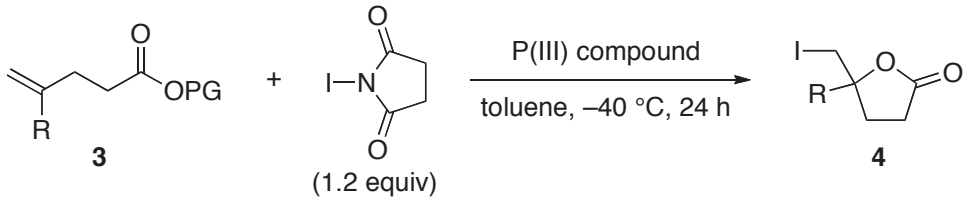
Scheme 2. Proposed catalytic cycle for the nucleophilic phosphine-catalyzed iodolactonization of **3a**

We chose 4-substituted 4-pentenoic acids **3** as model substrates for iodolactonization.[5] As a terminal group, *tert*-butyldimethylsilyl (TBDMS) ester would be suitable. As shown in Scheme 2, the TBDMS ester group of **3a** would react with the iodonium ion moiety of **5a**, and the TBDMS group would be spontaneously trapped by the succinimide anion to give iodolactone **4a**. According to our working hypothesis, we first examined the catalytic activity of PPh_3 toward the 5-*exo-trig* iodolactonization of **3a** (Table 1). The reaction was conducted with 1.2 equiv. of NIS in toluene at –40 °C. The catalytic activity highly depended on the amount of triphenylphosphine (PPh_3). Very interestingly, the best result (54% yield) was obtained when 30 mol% of PPh_3 was used (entry 4). The use of larger amounts (40–100 mol%) of PPh_3 decreased the yield of **4a** (entries 5–7). Interestingly, the catalytic activities of highly nucleophilic PBu_3 and tri(cyclohexyl)phosphine [$P(c\text{-}C_6H_{11})_3$] were quite low (entries 8 and 9) in contrast to the iodocyclization of 4-homogeranyltoluene (Scheme 1). Triphenyl phosphite [$P(OPh)_3$] showed a slightly higher activity than PPh_3 (entry 10).

Based on our preliminary work, it is conceivable that the reactivity of **3** depends on the terminal functional group. The reactivity of *tert*-butyl ester **3b** was slightly lower than that of TBDMS ester **3a**.

The reaction of **3b** proceeded at –20 °C and gave **4b** in 49% yield (entry 11). We next examined the catalytic iodolactonization of TBDMS ester of 4-substituted 4-pentenoic acids **3c**–**3f**. The reaction was conducted with NIS (1.2 equiv) in the presence of PPh_3 (30 mol%) in toluene. Compound **3c** (R = H), which has a monosubstituted carbon–carbon double bond, showed low reactivity and gave **4b** in 34% yield, even though the reaction was conducted at 0 °C (entry 12). In contrast, compounds **3d**–**3f**, which have 1,1-disubstituted carbon–carbon double bonds, were successfully converted to **4d**–**4f** at –40 °C (entries 13–15). In particular, compound **3d** bearing a less bulky methyl group at the 4-position showed good reactivity (entry 13). The high nucleophilicity of the carbon–carbon double bond in **3** would be important for obtaining **4** in high yield.

Table 1. Catalytic Activities of Nucleophilic Phosphorous Compounds Toward the Iodolactonization of **3**

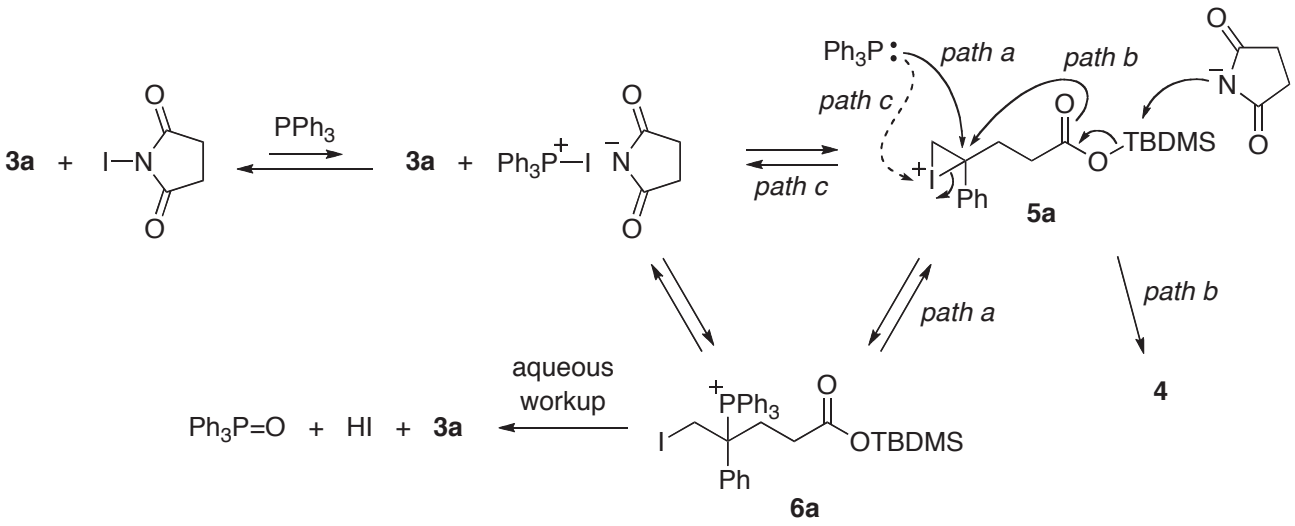


Entry	Substrate **3** (R, PG)	P(III) Compound [mol%]	Yield (%) of **4**
1	**3a** (Ph, TBDMS)	—	0
2	**3a** (Ph, TBDMS)	PPh_3 [10]	3
3	**3a** (Ph, TBDMS)	PPh_3 [24]	33
4	**3a** (Ph, TBDMS)	PPh_3 [30]	54
5	**3a** (Ph, TBDMS)	PPh_3 [40]	14
6	**3a** (Ph, TBDMS)	PPh_3 [60]	6
7	**3a** (Ph, TBDMS)	PPh_3 [100]	0
8	**3a** (Ph, TBDMS)	PBu_3 [30]	6
9	**3a** (Ph, TBDMS)	$P(c\text{-}C_6H_{11})_3$ [30]	3
10	**3a** (Ph, TBDMS)	$P(OPh)_3$ [30]	65
11[a]	**3b** (Ph, *t*-Bu)	PPh_3 [30]	49
12[b]	**3c** (H, TBDMS)	PPh_3 [30]	34
13	**3d** (Me, TBDMS)	PPh_3 [30]	71
14	**3e** (Bn, TBDMS)	PPh_3 [30]	33
15	**3f** (c-C_6H_{11}, TBDMS)	PPh_3 [30]	59

[a] The reaction was conducted at –20 °C. [b] The reaction was conducted at 0 °C.

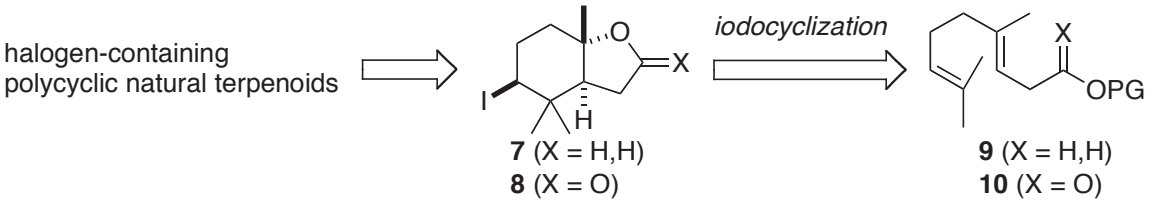
Although it is unclear why the use of large amounts of PPh_3 decreased their activity, we can propose the explanation in Scheme 3. When the reaction was conducted in the presence of 40–100 mol% of PPh_3, PPh_3 might attack the iodonium ion moiety of **5a** to give phosphonium ion intermediate **6a**, which would be converted back to **3a** by aqueous workup (*path a*).[6,7] Alternatively, the equilibrium between **3a** and **5a** might strongly favor the regeneration of **3a** in the presence of large amounts of PPh_3 (*path c*). In contrast, the intramolecular cyclization of **5a** successfully proceeded in the presence of 30 mol% of PPh_3

(*path b*), as shown in Scheme 2. The finding that highly nucleophilic phosphorous compounds showed low catalytic activities might also be explained by this mechanism.



Scheme 3

Many halogenated polycyclic terpenoids possessing a cyclic ether structure have been isolated from various marine organisms.[8] For example, the cytotoxic substance aplysistatin was isolated from the South Pacific Ocean sea hare *Aplysia angasi*.[9] Luzonenone and luzofuran were isolated from the red alga *Laurencia luzonensis*.[10] The biosynthesis of these natural products appears to include the halonium ion-induced polycyclization of linear isoprenoids bearing terminal oxygen groups.[11] Catalytic diastereoselective iodocyclization is one of the most promising methods for the chemical synthesis of these polycyclic natural compounds, since polycyclic iodoterpenoids can be converted to other halogenated derivatives by stereospecific transhalogenation.[3] Therefore, we next examined the nucleophilic phosphine-catalyzed iodocyclization of **9** and **10** (Scheme 4).

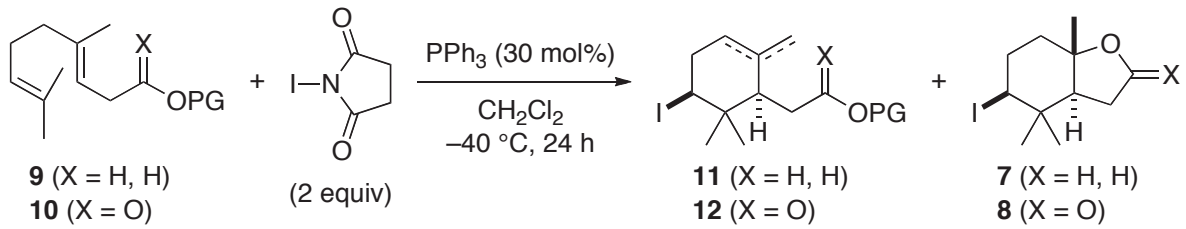


Scheme 4

First, the catalytic iodoetherification of *O*-protected homogeraniol **9** was examined (Table 2). The reaction was conducted with NIS in the presence of PPh_3 (30 mol%) in CH_2Cl_2.[12] When the reaction of TBDMS ether **9a** was conducted with 1.2 equiv. of NIS, the desired *trans*-fused dicyclic product **7** was

obtained in 35% yield as a single diastereomer (entry 1). To improve the yield of **7**, the reaction was conducted with 2.0 equiv. of NIS. As a result, **7** was successfully obtained in 68% yield along with a small amount of monocyclic product **11a** (15%) (entry 2). The reaction of *p*-methoxyphenyl (PMP) ether **9b** also proceeded to give monocyclic product **11b**, which was easily converted to **7** (52%, 3 steps from **9b**) by oxidative deprotection of the PMP group [$Ce(NH_4)_2(NO_3)_6$] followed by Brønsted acid-promoted cyclization ($SnCl_4$, $ClSO_3H$) (entry 3). The iodolactonization of homogeranic acid esters **10** was also catalyzed by triphenylphosphine to give the corresponding iodocyclic product **8** as a single diastereomer. As in the case of **3**, TBDMS ester **10a** was more reactive than *tert*-butyl ester **10c** and gave **8** in 47% yield along with monocyclic product **12a** (11%) (entries 4 and 5).

Table 2. Triphenylphosphine-Catalyzed Iodocyclization of Homogeraniol Derivatives **9** and Homogeranic Acid Derivatives **10**



9 (X = H, H)
10 (X = O)

11 (X = H, H)
12 (X = O)

7 (X = H, H)
8 (X = O)

Entry	Substrate (PG)	Yield (%)	
1[a]	**9a** (TBDMS)	**11**, 3	**7**, 35
2	**9a** (TBDMS)	**11**, 15	**7**, 68
3	**9b** (PMP)	**11**, —	**7**, 52[b]
4	**10a** (TBDMS)	**12**, 11	**8**, 47
5	**10c** (*t*-Bu)	**12**, 17	**8**, 22

[a] The reaction was conducted with NIS (1.2 equiv.). [b] The yield of **7** was evaluated after oxidative deprotection and Brønsted acid-promoted cyclization.

In conclusion, we investigated nucleophilic phosphine-catalyzed diastereoselective iodocyclization with oxygen terminal groups.[13] For the 5-*exo-trig* iodolactonization of TBDMS esters of 4-substituted 4-pentenoic acids **3**, 30 mol% of triphenylphosphine showed moderate catalytic activity under mild reaction conditions (toluene, –40 °C). TBDMS ether of homogeraniol and TBDMS ester of homogeranic acid were successfully converted to the corresponding iodopolycyclic products in the presence of a catalytic amount of triphenylphosphine with complete diastereoselectivity.

ACKNOWLEDGEMENTS

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6. Compound **3a** might be regenerated from **6a** through the nucleophilic attack on the iodine atom by OH^-, $S_2O_3^{2-}$ or something else.
7. ^{31}P NMR analysis of a 1:1:1 mixture of **3a**, NIS and PPh_3 did not show the generation of **6a** but only small amount (ca. 10%) of phosphonium salt $I–PPh_3^+$. The intermediate **6a** might be too moisture sensitive to be detected by NMR analysis.
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12. General procedure for the iodocyclization of homogeraniol derivatives **9** and homogeranic acid derivative **10**: To a solution of triphenylphosphine (30 mol%) and **9** or **10** (0.10 mmol) in CH_2Cl_2 (1 mL) was added NIS (2.0 equiv.) at –78 °C, and the mixture was stirred at –78 °C for 0.5 h and then at –40 °C for 24 h. The reaction mixture was quenched with $Na_2S_2O_3$ (3 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was dried over Mg_2SO_4, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography on silica gel

with a 30:1 mixture of hexane–EtOAc. **7**: oil; IR (neat) 2872, 1455, 1376, 1140, 1064, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 3H), 1.04 (s, 3H), 1.13 (s, 3H), 1.42–1.62 (m, 2H), 1.73 (m, 1H), 1.8–2.0 (m, 2H), 2.14–2.31 (m, 1H), 2.37–2.45 (m, 1H), 3.52–3.66 (m, 2H), 4.08 (dd, *J* = 4.2, 12.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 20.0, 25.7, 32.5, 35.5, 38.7, 40.9, 48.9, 54.3, 64.6, 78.9; HRMS (EI) calcd for $C_{11}H_{19}IO$ (M^+) 294.0481, found 294.0499. **8**: oil; IR (neat) 1772, 1457, 1387, 1188, 1132 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 6H), 1.39 (s, 3H), 1.78–1.92 (m, 2H), 2.09–2.59 (m, 5H), 4.08 (dd, *J* = 4.8, 12.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 20.4, 30.8, 32.0, 34.8, 38.2, 39.9, 44.7, 52.8, 84.8, 175.2; HRMS (EI) calcd for $C_{11}H_{17}IO_2$ (M^+) 308.0273, found 308.0285.

13. Triphenylphosphine could not be recovered because it was oxidized to triphenylphosphine oxide by unreacted NIS through aqueous workup.