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A Mild Method for Generation of *p*-Methoxybenzyl Cation through NIS-Mediated Activation of *p*-Methoxybenzyl 4-Pentenyl Ether

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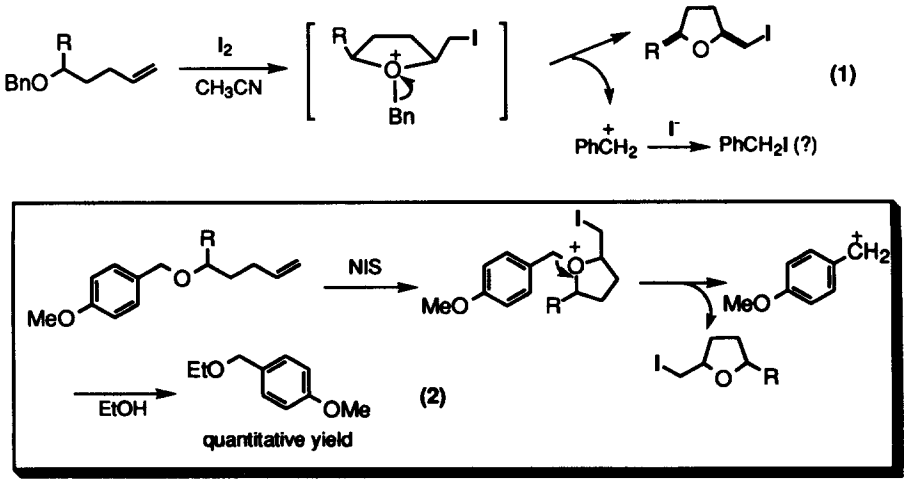
Abstract: A mild and facile method for generation of *p*-methoxybenzyl cation through NIS-mediated activation of *p*-methoxybenzyl 4-pentenyl ether was achieved. Under the present activation conditions, various alcohols were converted to the corresponding *p*-methoxybenzyl ethers. A scope and limitation of the present *p*-methoxybenzylation reaction was also investigated.

In 1981, Bartlett *et al.* reported that the reaction of appropriate benzyl 4-pentenyl ether derivatives with I_2 in CH_3CN provides tetrahydrofuran derivatives with high 2,5-*cis* -selectivity through loss of benzyl cation from the cationic haloetherification intermediate [Scheme 1 (1)].[1] Under this reaction conditions, the benzyl cation may be trapped by iodide to produce benzyl iodide. With reference to this report, during our investigation of haloetherification of 4-pentenyl ether derivatives under various conditions, we found that the reaction of *p*-methoxybenzyl 4-pentenyl ether with *N*-iodosuccinimide (NIS) in EtOH gives *p*-methoxybenzyl ethyl ether in a quantitative yield through *p*-methoxybenzyl cation generated from the cationic haloetherification intermediate [Scheme 1 (2)].[2] As a part of our project related to the development of synthetic organic reactions using an iodine-mediated activating process, we have focused our attention on the present activating mechanism.[3] This paper reports a mild and facile method for generation of *p*-methoxybenzyl cation through NIS-mediated

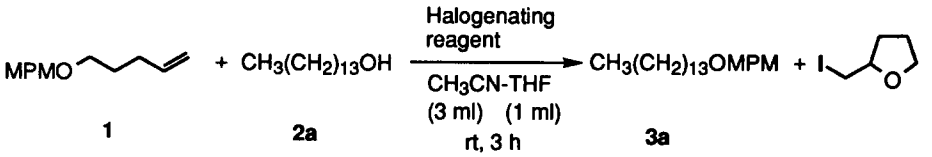
Scheme 1



activation of *p*-methoxybenzyl 4-pentenyl ether and, scope and limitation in *p*-methoxybenzylation of alcohols using this activating method.

After optimization of reaction conditions (Scheme 2, Table 1), it was found that alcoholysis of *p*-methoxybenzyl 4-pentenyl ether **1** proceeds in good yield (71 %) even with 1 equiv. of alcohol **2a** through NIS-mediated activating process in CH_3CN (Table 1, Entry 1). Although the use of excess **1** and NIS (1.5 and 1.8 equiv., respectively) resulted in increase in chemical yield (80 %), several side products which are relatively difficult to separate by column chromatography also produced (Entry 2). **1** completely disappeared even in the absence of alcohol **2a** within 3 h at room temperature to give several unidentified compounds which may be formed by the reaction of *p*-methoxybenzyl cation with CH_3CN. Therefore, when excess **1** and NIS are used as in the case of Entry 2, the side products may be resulted from the reaction with CH_3CN. The reaction with excess alcohol **2a** (2 equiv.) gave the best result, although the synthetic value would be lowered (Entry 3). The use of NBS as halogenating reagent led to the considerable decrease in chemical yield (48 %, Entry 4). The solvent effect in this reaction should be noted, that is, **1** was completely consumed within 3 h at room temperature in CH_3CN, while the reactions in other solvents (THF, toluene, DMF, $CHCl_3$) were not complete even after 24 h to give a mixture of the starting material **1**, **2a** and product **3a** (in the case of **2a**, THF was added as a cosolvent because of low solubility of **2a** in CH_3CN).

Scheme 2



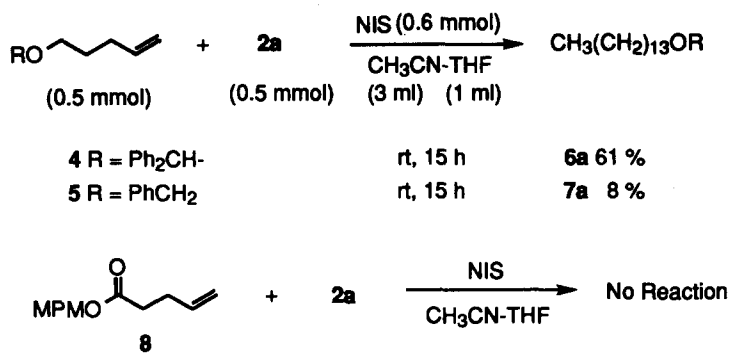
1 **2a** **3a**

Table 1 *p*-Methoxybenzylation of **2a**

Entry	**1** (mmol)	**2a** (mmol)	Reagent (mmol)	Yield of **3a** (%)
1	0.5	0.5	NIS, 0.6	71
2	0.75	0.5	NIS, 0.9	80
3	0.5	1.0	NIS, 0.6	91
4	0.5	0.5	NBS, 0.6	48

This activating method can be applied to generation of diphenylmethyl cation; the reaction of **4** with **2a** gave ether **6a** in 61% yield under the same conditions with those in Entry 1 of Table 1. In contrast, the reaction of benzyl ether **5** sluggishly proceeded due to the lower stability of the benzyl cation, compared with *p*-methoxybenzyl and diphenylmethyl cations to give a poor yield of **7a** together with recovery of a large amount of **5**. In the case of *p*-methoxybenzyl 4-pentenoate **8** which would proceed through a cationic halolactonization intermediate in the activating process, the starting materials were quantitatively recovered without the formation of any product.

Scheme 3



The *p*-methoxybenzyl group, which can be selectively deprotected by DDQ oxidation, is extensively utilized as a protective group of hydroxyl function in the synthesis of polyfunctionalized natural products.[4] *p*-Methoxybenzylation of the hydroxyl function is ordinarily achieved under basic[5] or acidic[6] conditions, while,

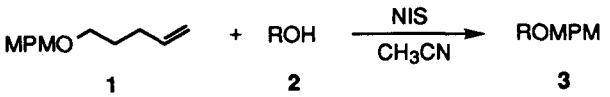
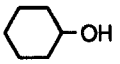
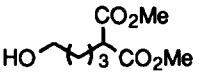
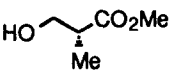
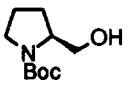


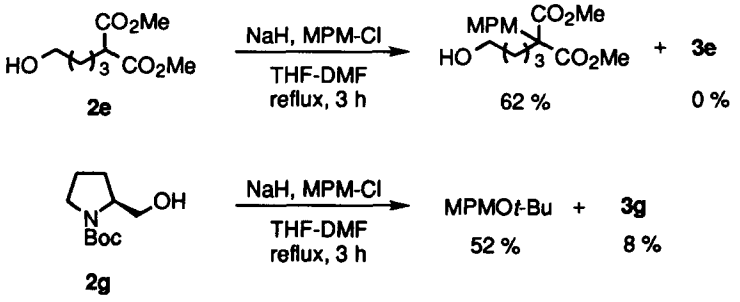
Table 2 *p*-Methoxybenzylation of alcohols[a]

Entry	ROH 2		Time (h)	ROMPM 3	Yield (%)[b]
1		2b	4	3b	60 (73)[c]
2		2c	1.5	3c	50 (56)[c]
3	$PhSO_2(CH_2)_5OH$	2d	5	3d	71
4		2e	5	3e	70
5		2f	5	3f	56 (72)[c]
6		2g	5	3g	71
7		2h	2.5	3h	64 (76)[d]
8	AcOH	2i	5	3i	44

a *p*-Methoxybenzylation: 1 (0.5 mmol), 2 (0.5 mmol), NIS (0.6 mmol), CH_3CN (3 ml), room temperature. *b* Isolated yield. *c* Numeral in the parentheses indicates the yield in the use of 2 equiv. of alcohol 2. *d* Numeral in the parentheses indicates the yield in the use of 2equiv. of 1 and NIS.

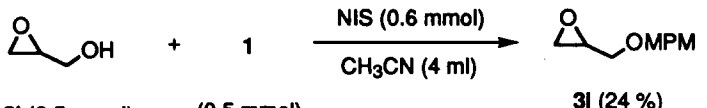
by this activating method, the formation of *p*-methoxybenzyl ether should be carried out under neutral conditions. Therefore, scope and limitation of the reactions with various alcohols using the present activation were further examined. The results are summarized in Table 2 and Scheme 5. The reaction of secondary or tertiary alcohol **2b**, **2c** also gave *p*-methoxybenzyl ether **3b**, **3c** in the presence of NIS in CH_3CN, although the yields were slightly lower than that of primary alcohol **2a** (Table 2, Entries 1, 2). Even if acidic α-hydrogen exists in the same molecule as in the case of **2d**, **2e** and **2f** (especially, **2e** having an active methine hydrogen), the corresponding *p*-methoxybenzyl ethers **3d**, **3e** and **3f** can be obtained in good yields (Entries 3, 4, 5). In contrast, *p*-methoxybenzylation of **2e** under usual basic conditions gave *C*-benzylation product as a major product without the formation of MPM ether **3e** (Scheme 4). The reaction of optically pure alcohol **2f** proceeded without β-elimination and racemization to give **3f**.[7] Due to the neutral conditions, this activating method is applicable to *N*-Boc prolinol **2g** to give **3g** in good yield (Entry 6), while in the reaction of **2g** under basic conditions, **3g** was obtained in 8 % yield together with a large amount of *p*-methoxybenzyl *t*-butyl ether (Scheme 4). The present method can be applied to decenol **2h** having olefinic group to give **3h** in good yield (Entry 7). The reaction of acetic acid **2i** gave a lower yield of ester **3i** due to the reduced nucleophilicity of carboxylate compared with alcohols (Entry 8). In the present reaction, the use of 2 equiv. of alcohols **2** often led to increase in the chemical yield (Entries 1, 2, 5), therefore, if the alcohols **2** can be easily recovered, the use of excess **2** may be recommended. With substrates **2h** and **2a**, although slight increase in the chemical yields was observed by using excess of NIS and **1** (Entry 7 in Table 2, Entry 2 in Table 1), unidentified side products were also formed in addition to the MPM ether **3**.

Scheme 4

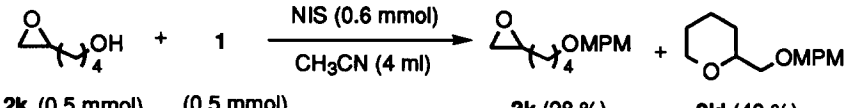


This activating method was not effective in *p*-methoxybenzylation of epoxyalcohol derivatives. For example, the reaction of glycidol **2j** under the same conditions gave the ether **3j** in a low yield (24 %) with the recovery of starting material **2j** (Scheme 5). In the reaction of epoxyalcohol **2k**, tetrahydropyran derivative **3k'** along with **3k** was obtained as a major product (Scheme 5). The reaction of hexafluoro-2-propanol **2l** and 2-phenyl-3-octyn-2-ol **2m** resulted in complex mixture without the formation of the corresponding *p*-methoxybenzyl ether due to decrease of nucleophilicity of alcohols by electronic or steric factor. In these cases, the nucleophilic attack of CH_3CN instead of hydroxyl group to *p*-methoxybenzyl cation intermediate may occur. In the reaction of *N*-Cbz-serine **2n**, *p*-methoxybenzylation of carboxyl and amino group proceeded to give the complicated products.

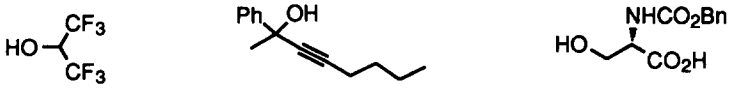
Scheme 5



2j (0.5 mmol) (0.5 mmol) **3j** (24 %)



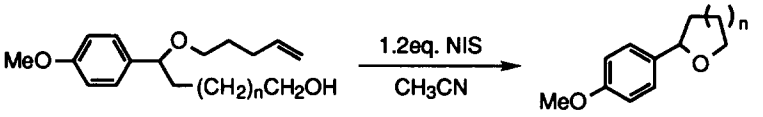
2k (0.5 mmol) (0.5 mmol) **3k** (28 %) **3k'** (40 %)



2l **2m** **2n**

An extension of the present activation to intramolecular reactions is shown in Scheme 6. The reactions of pentenyl ethers **9a** and **9b** having a hydroxyl group in the same molecule proceeded in good yields to give tetrahydrofuran and tetrahydropyran derivatives **10a, 10b**, respectively.[8] Although the chemical yield is moderate, the reaction of pentenyl ether **9c** also gave 7-membered ring ether **10c**.

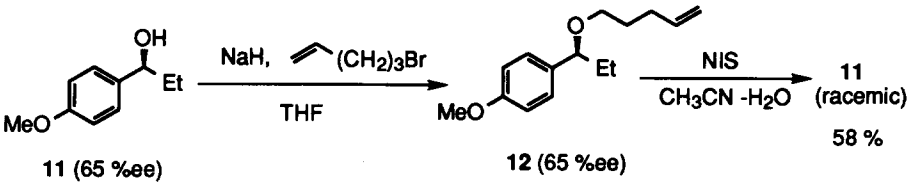
Scheme 6



9a n=1	rt, 2.5 h	**10a** 74 %
9b n=2	rt, 1.5 h	**10b** 73%
9c n=3	rt, 5 h	**10c** 41 %

With regard to the mechanism of this activating process, the hydrolysis of optically active ether **12** was examined under the same conditions (Scheme 7).[9,10] The formation of racemic alcohol **11** may indicate that the reaction of pentenyl ether derived from secondary *p*-methoxybenzyl alcohol proceeds in S_N1-like mechanism which invloves the generation of *p*-methoxybenzyl cation in this case.

Scheme 7



In conclusion, we have shown a mild method for generation of *p*-methoxybenzyl cation through NIS-mediated activating process and a facile *p*-methoxybenzylation of various alcohols using this activating method.

Experimental Section

^1H and ^{13}C NMR spectra were recorded on a 400- and 300-MHz spectrometer. In ^1H and ^{13}C NMR spectra, chemical shifts were expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm) and $CDCl_3$ (77.0 ppm), respectively. Mass spectra were recorded by electron impact. Column chromatography was performed on a silica gel, Wakogel C-200 (75-150 μm). Medium-pressure liquid chromatography (MPLC) was performed on a 30 x 4 cm i. d. prepacked column (silica gel, 50 μm) with a UV detector.

Genaral procedure for *p*-methoxybenzylation reaction

To a mixture of 5-phenylsulfonyl-1-pentanol **2d** (114 mg, 0.5 mmol) and *p*-methoxybenzyl 4-pentenyl ether **1** (103mg, 0.5 mmol) in CH_3CN (4 ml) was added *N*-iodosuccinimide (135 mg, 0.6 mmol) at room temperature. After being stirred for 2 h at the same temperature, the mixture was poured into $Na_2S_2O_3$ solution and extracted with AcOEt. The AcOEt extracts were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (hexane:AcOEt=3:1) to afford 124 mg (71 %) of **3d**.

The spectra data of unknown compounds are as follows.

1-*p*-Methoxybenzyl 5-phenylsulfonylpentyl ether (3d) **3d**: colorless oil: IR (neat) 3002, 2937 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.40-1.81(m, 6H), 3.10 (m, 2H), 3.42 (t, J = 6.1 Hz, 2H), 3,82 (s, 3H), 4.41 (s, 2H), 6.89 (d, J = 8.5 Hz, 2H), 7.24 (d, J = 8.5Hz, 2H), 7.59 (t, J = 6.8 Hz, 2H), 7.68 (m, 1H), 7.91 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 22.5, 25.1, 29.1, 55.3, 56.2, 69.4, 72.6, 113.8, 128.0, 128.6, 129.2, 130.5, 133.6, 139.2, 159.2; MS (m/z) 348 (M^+), 227, 211, 179, 169. Anal. Calcd for $C_{19}H_{24}O_4S$: C, 65.49, H, 6.94. Found: C, 65.19, H, 7.03.

Dimethyl 4-*p*-methoxybenzyloxybutylmalonate (3e) Compound **3e** was prepared from **2e** (114 mg, 0.5 mmol) in accordance with general procedure. Purification by column chromatography (hexane/AcOEt= 10:1) gave **3e** (113 mg, 70 %). **3e**: colorless oil: IR (neat) 2927, 2854, 1771 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.35-1.45 (m, 2H), 1.58-1.68 (m, 2H), 1.88-1.97 (m, 2H), 3.36 (t, J = 7.6 Hz, 1H), 3.43 (t, J = 6.5 Hz, 2H), 3.73 (s, 6H), 3.80 (s, 3H), 4.41 (s, 2H), 6.86 (d, J = 8.4 Hz, 2H), 7.24 (d, J = 8.4 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 24.0, 28.5, 29.2, 51.6, 52.3, 55.1, 69.4, 72.4, 113.7, 129.1, 130.5, 159.0, 169.7; MS (m/z) 324 (M^+), 137, 121. Anal. Calcd for $C_{17}H_{24}O_6$: C, 62.95, H, 7.46. Found: C, 62.70, H, 7.62.

(*S*)-*N*-*tert*-Butoxycarbonyl-2-*p*-methoxybenzyloxymethylpyrrolidine (3g) Compound **3g** was prepared from **2g** (101 mg, 0.5 mmol) in accordance with general procedure. Purification by column chromatography (hexane:AcOEt=10:1) geve **3g** (113 mg, 71 %). **3g**: colorless oil: IR (neat) 2974, 2874, 1695 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.44 (s, 9H), 1.73-2.02 (m, 4H), 3.20-3.45 (m, 3H), 3.50-3.68 (m, 1H), 3.80 (s,

3H), 3.82-4.05 (m, 1H), 4.51 (bs, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 22.9, 23.7, 28.5, 46.3. 55.2, 56.5, 70.7, 72.8, 79.1, 113.7, 129.0, 130.5, 154.5, 159.1.; MS (m/z) 321 (M^+), 264, 221, 220, 185, 170. Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26, H, 8.47. Found: C, 66.91, H, 8.64.

General procedure for intramolecular reaction

To a solution of **9a** (118 mg, 0.45 mmol) in CH_3CN (4 ml) was added *N*-iodosuccinimide (122 mg, 0.54 mmol) at room temperature. After being stirred for 2.5 h at the same temperature, the mixture was poured into NaS_2O_3 solution and extracted with AcOEt. The AcOEt extract was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography (hexane:AcOEt=30:1) to afford 59 mg (74 %) of **10a**.

2-*p*-Methoxyphenyltetrahydrofuran (10a) **10a**: colorless oil; IR ($CHCl_3$) 2984, 2836 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.70-1.86 (m, 1H), 1.92-2.08 (m, 2H), 2.20-2.33 (m, 1H), 3.80 (s, 3H), 3.89 (ddd, J = 6.4, 8.0, 8.0 Hz, 1H), 4.09 (ddd, J = 6.9, 8.0, 8.0 Hz, 1H), 4.83 (t, J = 7.2 Hz, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 26.0, 34.4, 55.2, 68.4, 80.4, 113.7, 126.9, 135.3, 158.8; MS (m/z) 178 (M^+), 147, 135. Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13, H, 7.92. Found: C, 73.98, H, 8.00.

2-*p*-Methoxyphenyltetrahydropyran (10b) Compound **10b** was prepared from **9b** (140 mg, 0.5 mmol) in accordance with general procedure. Purification by column chromatography (hexane:AcOEt=40:1) and then MPLC (hexane:AcOEt=50:1) gave **10b** (70 mg, 73 %). **10b**: colorless oil; IR ($CHCl_3$) 2936, 2838 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.50-2.00 (m, 6H), 3.61 (dt, J = 2.2, 11.4 Hz, 1H), 3.79 (s, 3H), 4.11 (ddd, J = 1.7, 2.3, 11.4 Hz, 1H), 4.27 (dd, J = 2.5, 10.4 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 24.0, 25.9, 33.8, 55.2, 69.0, 79.7, 113.6, 127.1, 135.5, 158.8; MS (m/z) 192 (M^+), 161, 135, 108. Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97, H, 8.39. Found: C, 74.90, H, 8.49.

2-*p*-Methoxyphenylhexahydrooxepin (10c) Compound **10c** was prepared from **9c** (146 mg, 0.5 mmol) in accordance with general procedure. Purification by column chromatography (hexane:AcOEt=50:1) and then MPLC (hexane:AcOEt=50:1) gave **10c** (42 mg, 41 %). **10c**: colorless oil; IR (neat) 3004, 2860 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.55-1.97 (m, 7H), 2.00-2.12 (m, 1H), 3.71 (ddd, J = 4.1, 7.4, 12.3 Hz, 1H), 3.78 (s, 3H) 3.94 (ddd, J = 4.4, 6.4, 12.3 Hz, 1H), 4.52 (dd, J = 3.8, 9.4 Hz, 1H), 6.87 (d, *J* = 9.0 Hz, 2H), 7.28 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 25.8, 26.7, 31.0, 37.8, 55.2, 68.6, 81.0, 113.5, 126.8, 136.8, 158.5; MS (m/z) 206 (M^+), 175, 163, 147, 135, 121. Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69, H, 8.79. Found: C, 75.48, H, 8.83.

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10. The *ee* of **11** and **12** was determined by HPLC analysis using Daicel CHIRALCEL OD column (4.6 x 250 mm; detection, 254-nm UV light). **11**: eluent, 3% 2-propanol in hexane; flow rate, 1.0 ml/min; retention time (min), *R* isomer 18.5, *S* isomer 20.5. **12**: 0.1 % AcOEt in hexane; 1.0 ml/min; *S* isomer 8.9, *R* isomer 10.0.

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