A SIMPLE SYNTHETIC METHOD FOR FLUORINE-CONTAINING 4*H*-PYRANO[3,2-*d*]ISOXAZOLES AND 4-CYANOETHYL-ISOXAZOLES FROM 5-TRIFLUOROACETYL-2-METHOXY-3,4-DIHYDRO-2*H*-PYRAN WITH HYDROXYLAMINE HYDROCHLORIDE

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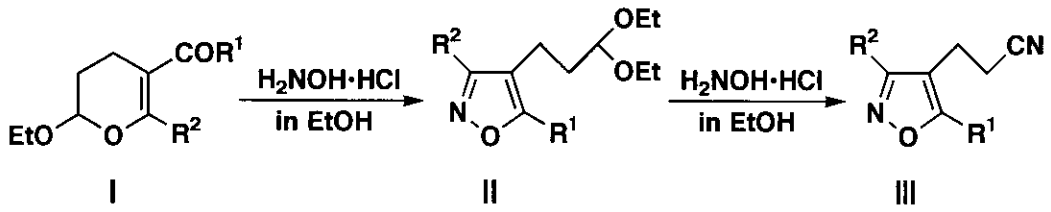
Abstract - 5-Trifluoroacetyl-2-methoxy-3,4-dihydro-2*H*-pyran (**1**), prepared from 2-methoxy-3,4-dihydro-2*H*-pyran with trifluoroacetic anhydride, reacted cleanly with hydroxylamine hydrochloride in alcohol to give fluorine-containing 4*H*-pyrano[3,2-*d*]isoxazoles (**2a-g**) or 4-cyanoethyldihydroisoxazoles (**3**) selectively in moderate to high yields. Further conversion of **3** into 4-cyanoethyl-isoxazoles (**4**) was also described.

In recent years considerable attention has been focused on the development of new methodologies for the synthesis of various fluorine-containing heterocycles, since these compounds are now widely recognized as important organic materials showing interesting biological activities for their potential use in medicinal and agricultural scientific fields.[1] As a part of our systematic research program on the simple syntheses of CF_3-containing heterocyclic compounds, thus far we have found that fluorine-containing pyrroles,[2a] pyrazoles,[2b] pyridines,[2c,d] pyrimidines,[2e] and 3,4-dihydro-2*H*-pyrans[2f,g] can be synthesized efficiently by making good use of the nucleophilic substitutions[3] at the olefinic carbon atoms and hetero Diels-Alder reaction[2f,g] of trifluoroacetylated alkenes. Recently, Yamauchi *et al.* have reported a novel and regioselective synthesis of 4-cyanoethylisoxazoles (Ⅲ) *via* unstable precursors (Ⅱ) from nonfluorinated 5-acyl-2-ethoxy-3,4-dihydro-2*H*-pyrans (Ⅰ) and hydroxylamine hydrochloride (Scheme 1).[4a] This situation prompted us to synthesize the title isoxazoles bearing trifluoromethyl group simply by the reaction of fluorinated 3,4-dihydro-2*H*-pyran (**1**) with hydroxylamine hydrochloride in alcohol. These new fluorine-containing isoxazoles are expected to show interesting pharmacological activities as psychotropic, antitumor antibiotic, and seed germination inhibitor.[5]

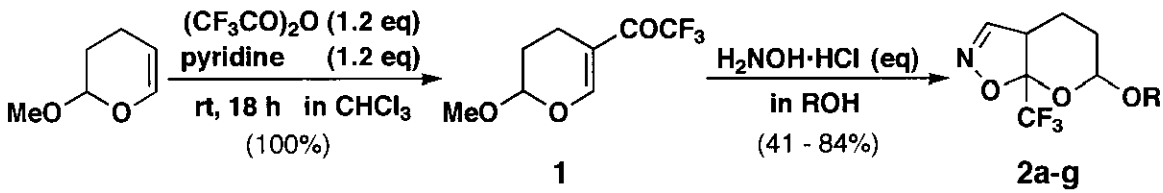


I II III

Scheme 1

5-Trifluoroacetyl-2-methoxy-3,4-dihydro-2*H*-pyran (**1**) was very easily prepared in a quantitative yield through the reaction of commercially available 2-methoxy-3,4-dihydro-2*H*-pyran with trifluoroacetic anhydride in the presence of pyridine at room temperature according to our method for trifluoroacetylation of electron- rich alkenes reported previously (Scheme 2).[6]

Reaction of **1** with an equimolar amount of hydroxylamine hydrochloride in methanol proceeded cleanly at room temperature to give the unexpected bicyclic dihydroisoxazoles, 7a-trifluoromethyl-6-methoxy-3a,5,6,7a-tetrahydro-4*H*-pyrano[3,2-*d*]isoxazole (**2a**), in 79% yield without producing the expected



Scheme 2

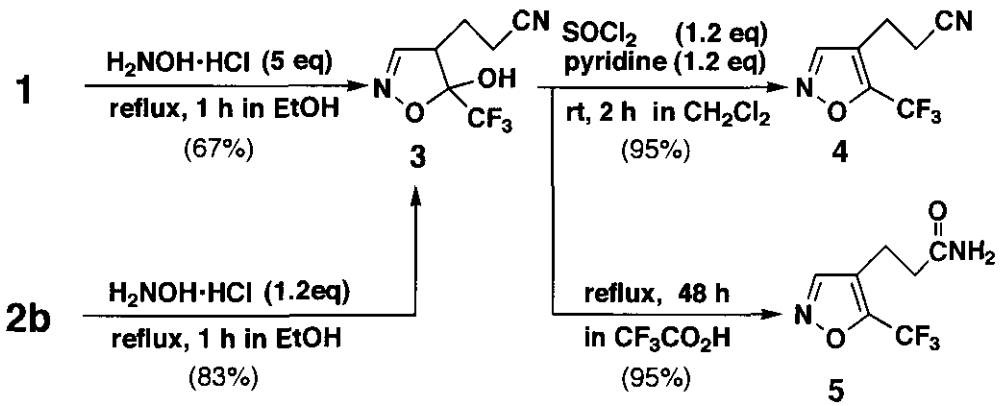
Table1. Reaction of **1** with Hydroxylamine Hydrochloride in Alcohols (ROH)

Entry	R	Temp (℃)	Time (h)	Product	Yield (%)[a)]
1	Me	rt	120	**2a**	79
2	Et	rt	48	**2b**	68
3	Pr	30	48	**2c**	67
4	Bu	30	48	**2d**	59
5	$H_2C{=}CHCH_2$	rt	24	**2e**	84
6	$HC{\equiv}CCH_2$	rt	24	**2f**	52
7	Bn	rt	48	**2g**	41

a) Isolated yields.

monocyclic isoxazoles such as || (R^1=CF_3, R^2=H, Me instead of Et), as shown in Scheme 2 and summarized in Table 1. In the cases with ethyl, propyl, and butyl alcohols as solvent, the corresponding 6-alkoxy derivatives (**2b-d**) were obtained in 59-68% yield. More highly functionalized 6-allyloxy and propargyloxy derivatives (**2e**,**f**) were also synthesized readily in 84% and 52% yields with allyl and propargyl alcohols, respectively, without any formation of polymerized tarry products. The reaction by the use of benzyl alcohol proceeded to afford the desired 6-benzyloxy derivative (**2g**) in 41% yield. However, attempts to synthesize 6-aryloxy derivatives by carrying out the present reactions in phenol were unsuccessful.

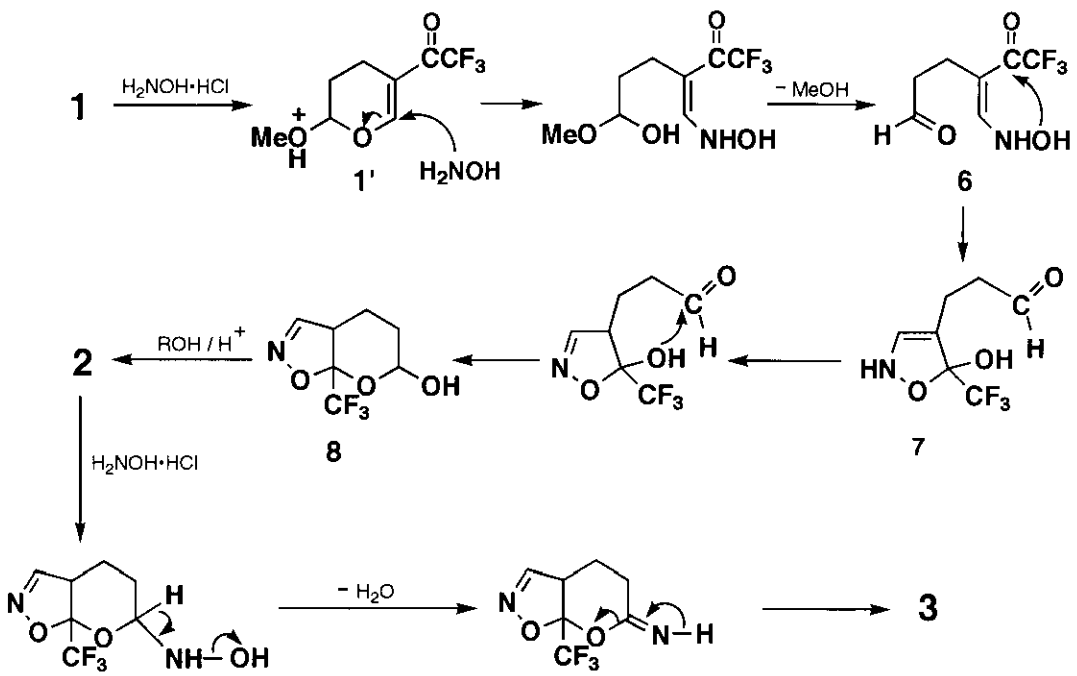
Next we attempted to run the present reaction by the use of a large excess of hydroxylamine hydrochloride in order to obtain fluorine-containing 4-cyanoethylisoxazoles (**3**, **4**). For example, reaction of **1** with 5 mole equivalents of hydroxylamine hydrochloride in refluxing ethanol for 1 h provided only stable dihydroisoxazoles (**3**) in 67% yield without being accompanied by the corresponding dehydrated compound, isoxazoles (**4**), in spite of the heating at 78 ℃ (Scheme 3). Pyranoisoxazoles (**2b**) was also found to react cleanly with 1.2 mole equivalents of hydroxylamine hydrochloride under the same conditions to give **3** in 83% yield. Furthermore, we succeeded in converting **3** into **4** effectively by HO-Cl exchange reaction and subsequent elimination of hydrochloric acid using thionyl chloride in the presence of pyridine. Treatment of **3** with trifluoroacetic acid under reflux for 48 h caused not only the desired dehydration but also acid-catalyzed hydrolysis of nitrile into amide to afford propanamides (**5**) in 95% yield.



Scheme 3

A possible mechanism for the present isoxazole ring forming reaction is as shown in Scheme 4. The initial nucleophilic attack by NH_2OH to olefinic C-6 atom of protonated dihydropyran (**1'**), which is regarded as α-carbon of β-trifluoroacetylvinyl ether system, occurs to give an intermediate O-N exchanged product,

β-trifluoroacetylenamine (**6**).[3] Dihydroisoxazole (**7**) is produced by intramolecular nucleophilic attack by OH of **6** to the carbonyl carbon of the trifluoroacetyl group. Subsequent enamine-imine tautomerism (1,3-H shift) and intramolecular nucleophilic attack by OH to the formyl carbon result in the formation of pyranoisoxazole (**8**), followed by acid-catalyzed HO-OR exchange on its hemiacetal carbon atom to afford **2**. Conversion of the acetal (**2**) into the nitrile (**3**) presumably proceeds by a mechanism analogous to that reported previously by Yamauchi.[4b]

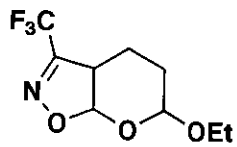


Scheme 4

The structures of all new compounds (**1**-**5**) were determined on the basis of their ^{1}H-NMR and IR spectra, together with elemental analyses. As a representative case, pyranoisoxazole (**2b**) was further confirmed by ^{13}C-NMR spectral data. All of them, except the signal [δ = 15.1 (q)] of methyl carbon of ethoxy group at the 6-position, appeared in pairs, which revealed the existence of two diastereoisomers. Moreover, it showed characteristic signals for the two acetal sp^3-carbons; one is C-7a bearing a CF_3 group at δ = 101.6 (q, J_{CF} = 34.2 Hz) or 103.4 (q, J_{CF} = 34.2 Hz), the other is C-6 at δ = 96.8 (d) or 98.1 (d). Combining this with other data presented unambiguous evidence supporting the corresponding bicyclic structure (fusion of dihydroisoxazole and tetrahydropyran rings) and excluded the possibility for the formation of its

regioisomer (**2b'**).

Thus, the present method provides a simple and efficient access to CF_3-containing 4*H*-pyrano[3,2-*d*]isoxazoles and 4-cyanoethylisoxazoles, which are not easily obtained by other methods. Further researches into the convenient synthetic methods for fluorine-containing heterocycles by this type of ring transformation of dihydropyran (**1**) with another nucleophiles are currently under way and the results will be published in our forthcoming papers.



2b'

EXPERIMENTAL

Melting points were determined on an electrothermal digital melting point apparatus and are uncorrected. IR spectra were recorded on a Hitachi EPI-G3 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained with JEOL PMX 60SI and FX 90Q instruments using $CDCl_3$ as a solvent unless otherwise indicated. All chemical shifts are reported in ppm downfield from internal tetramethylsilane; coupling constants (J) are given in Hz. Elemental analyses were taken with a Yanaco CHN Corder MT-5 analyzer and were performed by the Microanalyses Center of Kyoto University. Chromatographic separations were carried out on a silica gel column (Fuji Silysia Chemical BW-127ZH; 100-270 mesh). All reagents were obtained commercially and used without further purification. Final purification of all products for elemental analyses was done by Kugelrohr distillation or recrystallization.

Synthesis of 5-Trifluoroacetyl-2-methoxy-3,4-dihydro-2*H*-pyran (1): To a stirred solution of 2-methoxy-3,4-dihydro-2*H*-pyran (1142 mg, 10 mmol) and pyridine (950 mg, 12 mmol) in $CHCl_3$ (15 mL) was added dropwise trifluoroacetic anhydride (2520 mg, 12 mmol) with cooling and the stirring was continued at rt for 18 h. After addition of CH_2Cl_2 (100 mL), the mixture was washed with 1N HCl (100 mL), with saturated aqueous solution of Na_2CO_3 (50 mL), thoroughly with water (100 mL), and then dried (Na_2SO_4). The solvent was evaporated to give the practically pure product **1** (2100 mg, 100%): oven temperature 60 ℃/2 mmHg; IR (film) 1680, 1605 cm^{-1}; ^{1}H-NMR 7.70 (br s, 1H, H-6), 5.13 (t, 1H, J=3, H-2), 3.53 (s, 3H, CH_3), 2.57-1.60 (m, 4H, H-3, -4). Anal. Calcd for $C_8H_9O_3F_3$: C, 45.72; H, 4.32; F, 27.12. Found: C, 45.92; H, 4.37; F, 27.01.

Synthesis of 6-Alkoxy-7a-trifluoromethyl-3a,5,6,7a-tetrahydro-4*H*-pyrano[3,2-*d*]-isoxazoles (2a-g); General Procedure: To a solution of **1** (210 mg, 1 mmol) in the appropriate alcohol (4 mL) was added hydroxylamine hydrochloride (70 mg, 1 mmol) and the solution was stirred at rt or 30 ℃ for 24-120 h. After evaporation of the solvent, CH_2Cl_2 (50 mL) was added to the residue and the solution was washed with saturated aqueous solution of Na_2CO_3 (50 mL) and with water (50 mL), and then dried (Na_2SO_4). The solvent was removed *in vacuo* and the crude product was chromatographed using hexane/EtOAc (4:1) as an eluent to give **2a-g**.

2a: oven temperature 65 ℃/2 mmHg; IR (film) 1605 cm^{-1}; ^{1}H-NMR 7.16 (s, 1H, H-3), 5.05-4.83 (m,

1H, H-6), 3.72-3.15 (m, 1H, H-3a), 3.46 (s, 3H, CH_3), 2.71-1.42 (m, 4H, H-4, -5). Anal. Calcd for $C_8H_{10}NO_3F_3$: C, 42.67; H, 4.48; N, 6.22. Found: C, 42.90; H, 4.52; N, 5.93.

2b: oven temperature 70 ℃/2 mmHg; IR (film) 1604 cm^{-1}; ^{1}H-NMR 7.13 (s, 1H, H-3), 5.08-4.82 (m, 1H, H-6), 4.17-3.25 (m, 3H, H-3a, OCH_2), 2.63-1.42 (m, 4H, H-4, -5), 1.17 (t, 3H, J=7, CH_3); ^{13}C-NMR 151.2 (d), 150.8 (d), 122.6 (q, J_{CF}=283.2), 122.4 (q, J_{CF}=283.2), 103.4 (q, J_{CF}=34.2), 101.6 (q, J_{CF}=34.2), 98.1 (d), 96.8 (d), 64.7 (t), 64.1 (t), 45.7 (d), 44.6 (d), 25.7 (t), 25.1 (t), 16.8 (t), 16.2 (t), 15.1(q). Anal. Calcd for $C_9H_{12}NO_3F_3$: C, 45.19; H, 5.06; N, 5.86; F, 23.83. Found: C, 45.28; H, 5.19, N, 5.81; F, 23.70.

2c: oven temperature 90 ℃/4 mmHg; IR (film) 1602 cm^{-1}; ^{1}H-NMR 7.13 (s, 1H, H-3), 5.07-4.83 (m, 1H, H-6), 4.03-3.20 (m, 3H, H-3a, OCH_2), 2.40-1.27 (m, 6H, H-4, -5, $C\underline{H}_2CH_3$), 0.92 (t, 3H, J=7, CH_3). Anal. Calcd for $C_{10}H_{14}NO_3F_3$: C, 47.43; H, 5.57; N, 5.53. Found: C, 47.39; H, 5.54, N, 5.56.

2d: oven temperature 95 ℃/3 mmHg; IR (film) 1602 cm^{-1}; ^{1}H-NMR 7.17 (s, 1H, H-3), 5.09-4.91 (m, 1H, H-6), 4.12-3.24 (m, 3H, H-3a, OCH_2), 2.73-0.63 (m, 11H, H-4, -5, $CH_2CH_2CH_3$). Anal. Calcd for $C_{11}H_{16}NO_3F_3$: C, 49.44; H, 6.03; N, 5.24. Found: C, 49.47; H, 5.80; N, 5.44.

2e: oven temperature 120 ℃/4 mmHg; IR (film) 1647, 1608 cm^{-1}; ^{1}H-NMR 7.17 (s, 1H, H-3), 6.23-5.61 (m, 1H, $C\underline{H}$=CH_2), 5.50-4.90 (m, 3H, H-6, CH=$C\underline{H}_2$), 4.53-3.83 (m, 2H, OCH_2), 3.72-3.28 (m, 1H, H-3a), 2.27-1.43 (m, 4H, H-4, -5). Anal. Calcd for $C_{10}H_{12}NO_3F_3$: C, 47.81; H, 4.82; N, 5.58. Found: C, 47.81; H, 4.65; N, 5.75.

2f: oven temperature 100 ℃/3 mmHg; IR (film) 3252, 1674, 1607 cm^{-1}; ^{1}H-NMR 7.49 (s, 1H, H-3), 5.42-5.14 (m, 1H, H-6), 4.43-4.23 (m, 2H, OCH_2), 3.87-3.29 (m, 1H, H-3a), 3.13-1.25 (m, 4H, H-4, -5), 2.43 (t, 1H, J=2, ≡CH). Anal. Calcd for $C_{10}H_{10}NO_3F_3$: C, 48.20; H, 4.05; N, 5.62. Found: C, 48.52; H, 4.10, N, 5.25.

2g: oven temperature 130 ℃/3 mmHg; IR (film) 1606 cm^{-1}; ^{1}H-NMR 7.34 (s, 5H, C_6H_5), 7.17 (s, 1H, H-3), 5.18-4.43 (m, 3H, H-6, OCH_2), 3.70-3.31 (m, 1H, H-3a), 2.83-1.45 (br, 4H, H-4, -5). Anal. Calcd for $C_{14}H_{14}NO_3F_3$: C, 55.81; H, 4.68; N, 4.65. Found: C, 55.72; H, 4.61, N, 4.41.

Synthesis of 4-Cyanoethyl-5-trifluoromethyl-5-hydroxy-4,5-dihydroisoxazole (3); *from Dihydropyran (1):* To a solution of **1** (1050 mg, 5 mmol) in ethanol (20 mL) was added hydroxylamine hydrochloride (1740 mg, 25 mmol) and the solution was stirred at reflux temperature for 1 h. The solvent was removed under reduced pressure and the crude product was chromatographed using hexane/EtOAc (4:1) as an eluent to afford **3** (697 mg, 67%).

from Pyranoisoxazole (2b): To a solution of **2b** (240 mg, 1 mmol) in ethanol (4 mL) was added hydroxylamine hydrochloride (84 mg, 1.2 mmol) and the solution was stirred at reflux temperature for 1 h. The solvent was removed under reduced pressure and the crude product was chromatographed to give **3**

(173 mg, 83%).

3: oven temperature 130 ℃/2 mmHg; IR (film) 3272, 2240, 1615 cm^{-1}; ^{1}H-NMR ($CDCl_3/CD_3CN$) 7.28 (s, 1H, H-3), 5.88-4.01 (br, 1H, OH), 3.58 (dt, 1H, J=1.8, 7, H-4), 2.86-2.32 (m, 2H, $CH_2C\underline{H_2}CN$), 2.23-1.85 (m, 2H, $C\underline{H_2}CH_2CN$). Anal. Calcd for $C_7H_7N_2O_2F_3$: C, 40.39; H, 3.39; N, 13.46. Found: C, 40.39; H, 3.34, N, 13.51.

Reaction of Dihydroisoxazole (3) with Thionyl Chloride: To a stirred solution of **3** (208 mg, 1 mmol) and pyridine (95 mg, 1.2 mmol) in CH_2Cl_2 (4 mL) was added dropwise thionyl chloride (143 mg, 1.2 mmol) with cooling and the stirring was continued at rt for 2 h. After addition of CH_2Cl_2 (50 mL), the mixture was washed with saturated aqueous solution of Na_2CO_3 (50 mL), with 1N HCl (50 mL), thoroughly with water (50 mL), and then dried (Na_2SO_4). The solvent was evaporated to afford the practically pure product **4** (181 mg, 95%): oven temperature 100 ℃/6 mmHg; IR (film) 2232, 1638 cm^{-1}; ^{1}H-NMR 8.40 (s, 1H, H-3), 3.12-2.88 (m, 2H, CH_2), 2.73-2.49 (m, 2H, CH_2). Anal. Calcd for $C_7H_5N_2OF_3$: C, 44.22; H, 2.65; N, 14.74. Found: C, 44.07; H, 2.73, N, 14.80.

Treatment of Dihydroisoxazole (3) with Trifluoroacetic Acid: A solution of **3** (208 mg, 1 mmol) in trifluoroacetic acid (4 mL) was stirred at reflux temperature for 48 h. After evaporation of the solvent, the resultant crude product was chromatographed using EtOAc as an eluent to give **5** (198 mg, 95%): mp 69-70 ℃ (hexane/$CHCl_3$), oven temperature 140 ℃/1 mmHg; IR (film) 3416, 3300, 1666, 1600 cm^{-1}; ^{1}H-NMR ($CDCl_3/CD_3CN$) 8.36 (s, 1H, H-3), 6.84-5.41 (br, 2H, NH_2), 3.04-2.80 (m, 2H, CH_2), 2.59-2.33 (m, 2H, CH_2). Anal. Calcd for $C_7H_7N_2O_2F_3$: C, 40.39; H, 3.39; N, 13.46. Found: C, 40.30; H, 3.45, N, 13.50.

REFERENCES

1. a) R. Filler, 'Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, London, 1979; b) R. Filler and Y. Kobayashi, 'Biomedicinal Aspects of Fluorine Chemistry, 'Kodansha & Elsevier Biomedical, Tokyo, 1982; c) J. T. Welch, *Tetrahedron*, 1987, **43**, 3123; d) R. Filler, Y. Kobayashi, and L. M. Yagupolskii, 'Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications,' Elsevier, Amsterdam, 1993.

2. a) E. Okada, R. Masuda, M. Hojo, and R. Yoshida, *Heterocycles*, 1992, **34**, 1435; b) E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, 1992, **34**, 791; c) E. Okada, R. Masuda, and M. Hojo, *Heterocycles*, 1992, **34**, 1927; d) E. Okada, T. Kinomura, Y. Higashiyama, H. Takeuchi, and M. Hojo, *Heterocycles*, 1997, **46**, 129; e) E. Okada, T. Kinomura, H. Takeuchi, and M. Hojo, *Heterocycles*, 1997, **44**, 349; f) M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1989, 215; g) M. Hojo, R. Masuda, and E. Okada, *Synthesis*, 1990, 347.

3. a) M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, and K. Morimoto, *Tetrahedron Lett.*,

1989, **30**, 6173 ; b) M. Hojo, R. Masuda, E. Okada, H. Yamamoto, K. Morimoto, and K. Okada, *Synthesis*, 1990, 195; c) M. Hojo, R. Masuda, and E. Okada, *Chem. Lett.*, 1990, 2095; d) M. Hojo, R. Masuda, E. Okada, and Y. Mochizuki, *Synthesis*, 1992, 455; e) E. Okada, R. Masuda, M. Hojo, and R. Inoue, *Synthesis*, 1992, 533.

4. a) M. Yamauchi, S. Akiyama, T. Watanabe, K. Okamura, and T. Date, *J. Chem. Soc., Chem. Commun.*, 1993, 17; b) M. Yamauchi, *Chem. Pharm. Bull.*, 1993, **41**, 2042.
5. a) P. Krogsgaard-Larsen, L. Brehm, and K. Schaumburg, *Acta Chem. Scand. (B)*, 1981, **35**, 311; b) D. G. Martin, D. J. Duchamp, and C. G. Chidester, *Tetrahedron Lett.*, 1973, 2549; c) T. Kusumi, C. C. Chang, M. Wheeler, I. Kubo, K. Nakanishi, and H. Naoki, *Tetrahedron Lett.*, 1981, **22**, 3451.
6. M. Hojo, R. Masuda, and E. Okada, *Tetrahedron Lett.*, 1986, **27**, 353 and references cited therein.

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