Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 5, No. 9, pp. 923-926, 1995
Elsevier Science Ltd
Printed in Great Britain
0960-894X/95 $9.50+0.00

0960-894X(95)00140-9

Preparation and Biological Evaluation of β-Trifluoromethyl-α,β-unsaturated Carbonyl Compounds

Noriyasu Shinohara, Takashi Yamazaki and Tomoya Kitazume*

Department of Bioengineering, Tokyo Institute of Technology
Nagatsuta, Midori-ku, Yokohama, Japan

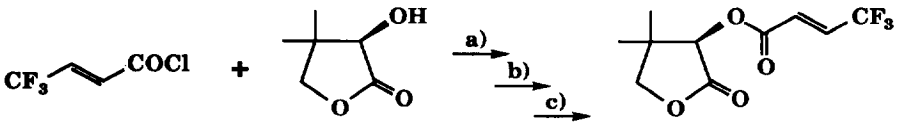
Abstract: β-Trifluoromethyl-α,β-unsaturated carbonyl compounds derived from (*E*)-3-(trifluoromethyl)acrylic acid **1** and D-(-)-pantoic acid lactone **3** and/or L-mannitol **5** were found to possess *in vitro* interleukin-2 antiproducing effect

Research on the incorporation of fluorine into organic molecules which can lead to profound and unexpected results on biological activity has been extensive in recent years.[1-4] Recently, we have reported that ethyl (*E*)-3-(trifluoromethyl)acrylate (**1**) is revealed to have significantly lower LUMO energy level than the corresponding nonfluorinated material and the similar value for the corresponding p_z orbital coefficients at the reaction sites, which demonstrated the higher reactivity of **(*E*)-1** as a Michael acceptor.[5] From our reported calculation results, β-trifluoromethyl-α,β-unsaturated carbonyl compounds are preferred due to its ability to act as an inhibitor.[6] Accordingly, we have been studying a new type of inhibitors possessing a β-trifluoromethyl-α,β-unsaturated carbonyl group. Herein, we report the synthesis of β-trifluoromethyl-α,β-unsaturated carbonyl compounds **4** and **7** and their interleukin-2 antiproducing effect.[7-11]

Treatment of (*E*)-3-(trifluoromethyl)acryloyl chloride (**2**) prepared from (*E*)-3-(trifluoromethyl)acrylic acid and thionyl chloride with (*R*)-3,3-dimethyl-4-butanolide (**3** : D-(-)-pantoic acid lactone) in Et_3N-CH_2Cl_2 system at room temperature gave (*R*)-2-*O*-(4,4,4-trifluoro-2-(*E*)-butenoyl)-3,3-dimethyl-4-butanolide (**4**) ($[\alpha]^{21}_D$ +5.49 (*c* 1.11, $CHCl_3$), >99% ee) in 96% yield after aqueous work-up followed by separation with silica gel column chromatography.

Furthermore, the synthesis of (*R*)-2-*O*-(4,4,4-trifluoro-2-(*E*)-butenoyl)-3,3-dimethyl-4-butanolide (**7**) ($[\alpha]^{18}_D$ +23.4 (*c* 1.09, $CHCl_3$), >99% ee) has been explored via the reaction of 1,2:5,6-*O*-diisopropylidene-*D*-mannitol (**6**) derived from D-mannitol and acetone in the presence of $ZnCl_2$, with (**2**) in *n*-BuLi-CH_2Cl_2 system at 0 °C.

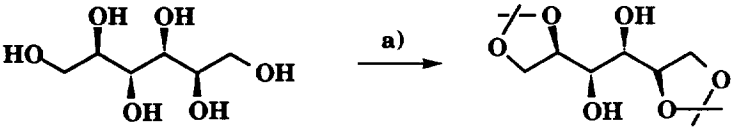
Scheme 1



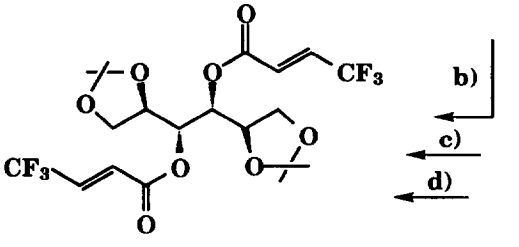
2 **3** **4**

a) 1.2 eq. Et_3N, CH_2Cl_2, 0 °C b) 0 °C ⟶ rt, overnight
c) quenched with aq. NH_4Cl

Scheme 2



5 **6**



7

a) $ZnCl_2$, CH_3COCH_3, rt b) *n*-BuLi, CH_2Cl_2, 0 °C,
(*E*)-CF_3CH=$CHCOCl$ c) 0 °C ⟶ rt, overnight
d) quenched with aq. NH_4Cl

For each of those compounds (4) and (7), the *in vitro* viable cell inhibitory towards interleukin-2 antiproducing effect was determined. The reported IC_{50} values represent the concentration of inhibitor producing 50 percent inhibition of interleukin-2 antiproducing effect. Table 1 gathers the results for compounds with the established interleukin-2 producing antimetabolite, cyclosporin A, as a reference. However, non fluorinated derivatives of compounds (4) and (7) retained no activity. Furthermore, A comparison of IC_{50} values demonstrated the potential of this β-trifluoromethyl-α,β-unsaturated carbonyl compound (7) as an interleukin-2 antiproducing substance, which interestingly showed effective nature. However, DTH suppressing effect of compound (7) retained no activity.

Table I Interleukin-2 Antiproducing Effect of Compounds (4 and 7) *in vitro* [a]

Compound No	IC_{50} (μg/mL)
Compound 4	3.71
Compound 7	0.8
Cyclosporin A	< 0.01

a) Cell was incubated in the presence or absence of compound. Then, MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide) was added for $OD^{578-588}$ measurements. IC_{50} (μg/mL) was given as the concentration at 50% inhibition of interleuki-2 producing.

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12) (*R*)-2-*O*-(4,4,4-Trifluoro-2-(*E*)-butenoyl)-3,3-dimethyl-4-butanolide (**4**): To a solution of (*R*)-3,3-dimethyl-4-butanolide (0.63 g, 4.8 mmol, >99% ee) and triethylamine (0.67 ml, 4.8 mmol) in methylene chloride (10 ml) was added 0.64 g (4.0 mmol) of 3-(trifluoromethyl)acryloyl chloride. After stirring overnight at room temperature, 1*N* HCl was added to the reaction mixture which was extracted with methylene chloride, washed with 1*N* HCl and diluted $NaHCO_3$, and dried over anhydrous $MgSO_4$, and purified by silica gel column chromatography (AcOEt:*n*-hexane = 1:4) in 96% yield: R_f=0.45 (AcOEt:*n*-hexane = 1:4), $([\alpha]^{21}_D$ +5.49 (*c* 1.11, $CHCl_3$), >99% ee). ^{1}H NMR d 1.17 (3 H, s), 1.25 (3 H, s), 4.10 (2 H, s), 5.46 (1 H, s), 6.62 (1 H, dq, $J_{H,H}$ = 15.80, 1.82 Hz), 6.91 (1 H, dq, $J_{H,H}$ = 15.80, 6.29 Hz). ^{13}C NMR d 19.91, 22.91, 40.42, 76.23, 121.79 (q, J = 270.0 Hz), 127.46 (q, J = 6.4 Hz), 133.14 (q, J = 35.7 Hz), 162.85, 171,67. ^{19}F NMR d 13.2 (d, $J_{F,H}$ = 4.85 Hz). IR (neat) n 1801, 1748 (C=O) cm^{-1}.

13) 3,4-Di-*O*-(4,4,4-trifluoro-2-(*E*)-butenoyl)-1,2,5,6-*O*-diisopropylidene-D-mannitol (**7**): To a solution of 1,2,5,6-*O*-di-isopropylidene-D-mannitol (3.54 g, 13.5 mmol) in methylene chloride (30 ml) was added 1.6 M *n*-butyllithium (11.9 ml, 29.7 mmol) under an atmosphere of nitrogen at 0 °C. After 30 min, this solution was treated with 5.12 g (32.3 mmol) of 3-(trifluoromethyl)acryloyl chloride. After stirring overnight at room temperature, aq. NH_4Cl solution was added to the reaction mixture which was extracted with methylene chloride, washed with diluted $NaHCO_3$, and dried over anhydrous K_2CO_3, and purified by silica gel column chromatography (AcOEt:*n*-hexane =1:5) in 61% yield: Physical properties of R_f=0.42 (AcOEt:*n*-hexane =1:5), $([\alpha]^{18}_D$ +23.4 (*c* 1.09, $CHCl_3$), >99% ee). ^{1}H NMR d 1.32 (3 H, s), 1.32 (3 H, s), 1.32 (3 H, s), 1.38 (3 H, s), 1.39 (3 H, s), 3.86 (2 H, dd, $J_{H,H}$ = 5.59, 8.62 Hz), 3.98 (2 H, dd, $J_{H,H}$ = 6.14, 8.61 Hz), 4.20 (2 H, m), 5.43 (2 H, m), 6.54 (2 H, dq, $J_{H,H}$ = 15.8, 1.84 Hz), 6.86 (2 H, dq, $J_{H,H}$ = 15.8, 6.32 Hz). ^{13}C NMR d 25.08, 26.51, 65.87, 72.66, 73.90, 109.97, 121.70 (q, J=271.2 Hz), 127.65 (q, J=6.0 Hz), 133.05 (q, J=35.7 Hz), 162.78. ^{19}F NMR d 12.9 (d, $J_{F,H}$ = 2.77 Hz). IR (neat) n 1744 (C=O) cm^{-1}.

(*Received in Japan* 30 *January* 1995; *accepted* 9 *March* 1995)