Pergamon

Tetrahedron 55 (1999) 10351–10364

TETRAHEDRON

Synthesis of the Water-Soluble Adenosine A_1 Receptor Antagonist FR166124 through a Novel Sequential Horner–Emmons / Isomerization Reaction

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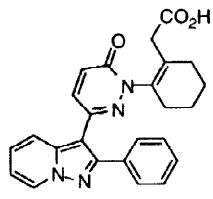
Received 7 June 1999; accepted 29 June 1999

Abstract: An efficient synthesis of FR166124 (**1**) was achieved through a novel sequential Horner–Emmons – isomerization reaction of cyclohexanone (**2**) with *tert*-butyl diethylphosphonoacetate (**3**) as the key process. Extensive studies of the key reaction indicated that temperature, base and conformation of the Horner–Emmons products were important factors in the isomerization reaction, leading to a proposed mechanism for this unusual Horner–Emmons reaction.

Keywords: Isomerization; Mechanisms; Wittig reactions; X-ray crystal structures

1. Introduction

Adenosine receptors are widely distributed throughout the human body and are classified into three major subtypes designated A_1, A_{2A} and A_3,[1–3] and many synthetic and pharmacological studies of adenosine A_1 receptor antagonists have been performed. It has been suggested that potent and selective adenosine A_1 receptor antagonists have the possibility to lead to therapeutic agents for certain kidney diseases.[2,4–6] The most serious problem encountered with selective adenosine A_1 receptor antagonists in this area has been low water solubility,[5,7] therefore, we have been searching for more potent, selective and water-soluble adenosine A_1 receptor antagonists.[8–10] We recently reported the discovery of FR166124 (**1**), which is a potent and highly selective adenosine A_1 receptor antagonist, and that the sodium salt of FR166124 has very high water



FR166124 (1)

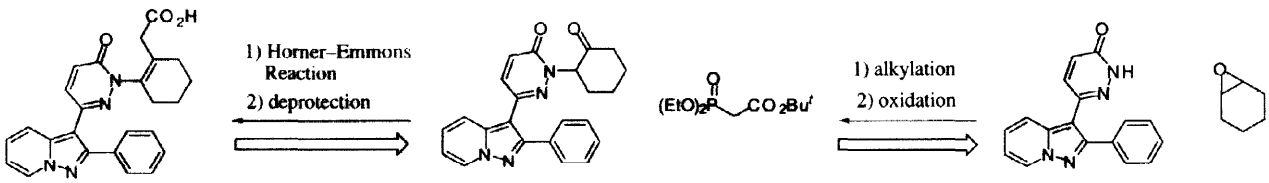
0040-4020/99/$ - see front matter
PII: S0040-4020(99)00590-6

solubility.[11] The next stage of preclinical evaluation of diuretic activity, vasodilating activity, and renal protective effect required large amounts of material, however, the low overall yield (7.5%, from **4**) in our first generation approach made it difficult to synthesize enough for pharmacological studies. Therefore, it was necessary to investigate a new efficient synthesis of **FR166124**. In this paper, an efficient synthesis of FR166124 based on a novel, sequential Horner–Emmons – isomerization reaction of cyclohexanone unit (**2**) with *tert*-butyl diethylphosphonoacetate (**3**), and the mechanism of this key reaction, is described.

2. Synthetic Strategy

Our new synthetic strategy for FR166124 involved the following two key reactions (Scheme 1). Firstly, coupling reaction of pyridazinone **4** with cyclohexene oxide (**5**) avoiding the formation of the competing *O*-alkylated product, which was observed in the case of coupling reaction of **4** with 2-chlorocyclohexanone.[11] Secondly, Horner–Emmons reaction and sequential isomerization reaction of **2** with *tert*-butyl diethylphosphonoacetate (**3**).

Scheme 1. Synthetic strategy of FR166124 (**1**).



1 : FR166124 **2** **3** **4** **5**

3. Results and Discussion

3-1. Synthesis of the Cyclohexanone unit (2).

According to our synthetic strategy, it was necessary to prepare the intermediate **2** effectively. Investigation of the alkylation of **4** with cyclohexene oxide (**5**) led to **6** which was obtained in up to 70% yield when NaH or *tert*-BuOK were used as a base in DMF. However, there was poor yield reproducibility in these reaction conditions (Table 1, Entries 1, 2). Therefore, we examined use of NaOH as a base and benzyltriethylammonium chloride as a phase-transfer catalyst in a refluxing mixture of toluene and water.[12] As a result, **6** could be obtained in 80% yield with good yield reproducibility when 3.0 equivalents of **5** and 1.15 equivalents of NaOH were used (Table 1, Entry 5). As shown in Table 1, 3.0 equivalents of **5** was required to obtain **6** in good yield and an excess amount of **5** greater than 3.0 equivalents did not improve yields further. Moreover, the yield of **6** was not improved when 1.5 equivalents of NaOH was used. Fortunately, **6** appeared as a solid in the reaction mixture; we could thus obtain **6** only by filtration of the reaction mixture and it was used in the

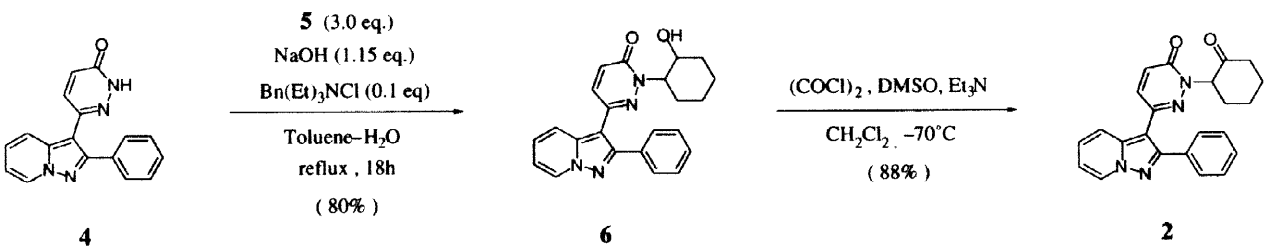
Table 1

Reaction of **4** with Cyclohexene oxide (**5**).

Entry	Reaction conditions	**5** (equiv)	Yield [a] (%)	Note
1	NaH (1.0 eq.) / DMF , 130 °C , 5h	1.2	70	poor reproducibility
2	*t*-BuOK (1.0 eq.) , 18-crown-6-ether (0.1 eq.) DMF , 130 °C , 8h	1.2	70	poor reproducibility
3	NaOH (1.0 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	1.2	55	30% of **4** was recovered
4	NaOH (1.0 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	3.0	65	**4** remained[b]
5	NaOH (1.15 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	3.0	80	trace of **4** remained[b]
6	NaOH (1.5 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	3.0	75	trace of **4** remained[b]
7	NaOH (1.15 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	4.5	75	trace of **4** remained[b]
8	NaOH (1.15 eq.) , $Bn(Et)_3NCl$ (0.1 eq.) Toluene–H_2O , reflux , 18h	6.0	76	trace of **4** remained[b]

a : Isolated yield.
b : Unreacted **4** was not recovered.

Scheme 2. Synthesis of the Cyclohexanone unit (**2**).



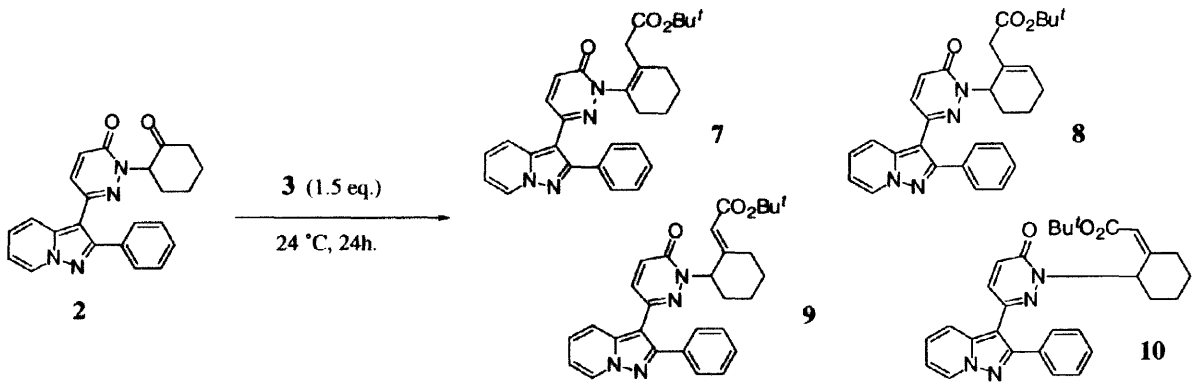
subsequent Swern oxidation without further purification. The cyclohexanone unit (**2**) could be obtained in 88% yield by Swern oxidation of **6** (Scheme 2).

3-2. Synthesis of FR166124 (1).

It is apparent that selective synthesis of **7** by Horner–Emmons reaction of **2** was of the most critical importance for an efficient successful synthesis of FR166124, since **7** is an unusual product of Horner–Emmons reaction.[13–15] In order to solve this problem, extensive studies of the Horner–Emmons reaction of **2**

Table 2

Horner–Emmons Reaction of **2** with *tert*-Butyl diethylphosphonoacetate (**3**).



Entry	Conditions		Product ratio[b] (%)				
	Base	Solvent	2	7	8	9	10
1	1.5 eq. *t*-BuOK[a]	THF	15.0	1.7	0.3	21.6	61.4
2	1.5 eq. NaH	THF	-----	65.8	0.2	23.5	10.5
3	1.5 eq. *t*-BuOK[a]	Toluene	6.5	34.1	1.8	16.0	41.6
4	1.5 eq. NaH	Toluene	-----	80.8	0.4	18.5	0.3
5	**3** (1.0 eq.), 1.0 eq. NaH	Toluene	29.0	6.0	-----	17.0	48.0
6	**3** (2.0 eq.), 2.0 eq. NaH	Toluene	-----	78.7	0.7	20.5	0.1
7	**3** (2.0 eq.), 2.0 eq. *t*-BuOK[a]	Toluene	-----	73.1	18.9	7.5	0.4

a : Catalytic amount of 18-crown-6-ether (0.1 equiv) was added.
b : Product ratio was determined by HPLC analysis.

were carried out. In the course of these studies, a number of reaction conditions were investigated by analysis of product ratio using high-performance liquid chromatography (HPLC), and results are summarized in Table 2, since all possible isomers (**7**, **8**, **9** and **10**) formed in this reaction could be isolated. As shown in Table 2, toluene was a more suitable solvent than THF. Despite the fact that **7** was produced in 73.1% yield using 2.0 equivalents of **3** and *tert*-BuOK, NaH was a more effective base than *tert*-BuOK since **7** was produced in 80.8% using 1.5 equivalents of **3** and NaH (Table 2, Entries 4, 7). Although toluene was a good solvent, the major products were *exo* isomers (**9**, **10**) and starting **2** remained when 1.5 equivalents of **3** and *tert*-BuOK was used as a base (Table 2, Entry 3). Furthermore, more than 1.5 equivalents of **3** and NaH were necessary for this reaction (Table 2, Entries 4, 6). In the case of using equimolar amounts of **3** and NaH, only 6% of **7** was produced; the *exo* isomers (**9**, **10**) were produced as major products and starting **2** remained (Table 2, Entry 5). Additionally, 1.5 equivalents of ethyl diethylphosphonoacetate, using NaH as a base in THF was also

effective, but **2** still remained. As a result, it was found that Horner–Emmons reaction of **2** with 1.5 equivalents of **3** using NaH as a base in toluene were the best conditions for selective synthesis of **7**, in spite of the necessity of separation of isomer **9** by SiO_2 column chromatography. Overall, **7** was obtained in 80% isolated yield as an unusual product of Horner–Emmons reaction (Scheme 3). Initially, the structures of the minor olefin isomers were assumed to be **9** and **10** based on the ^1H NMR spectroscopic properties. *Endo* isomer **8** displayed a signal at 2.82 ppm (ABq, 2H, J = 15.6, 15.5 Hz) for the methylene adjacent in the ester group and 6.06 ppm (br-s, 1H) for the proton at C2. Concerning the chemical shifts of the proton at C2 of *exo* isomers **9** (5.65 ppm, dd, 1H, J = 11.8, 3.1 Hz) and **10** (6.43 ppm, t, 1H, J = 4.2 Hz), a 0.78 ppm low-field shift of **10** was observed. It was assumed that this low-field shift resulted from the conformational differences between them (Figure 1). Considering the conformations of **9** and **10**, the proton at C2 of **10** is present in an equatorial position due to serious steric hindrance between the *tert*-butyl ester group and the pyridazinone moiety (**10a**).

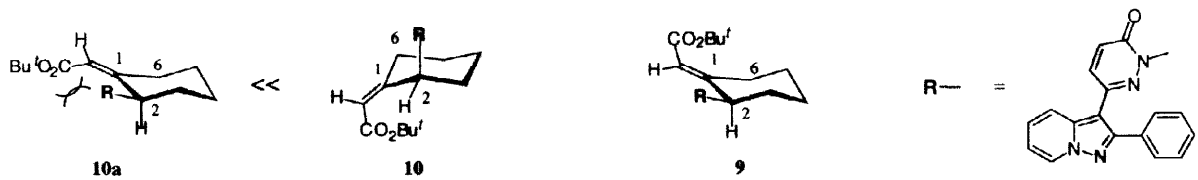
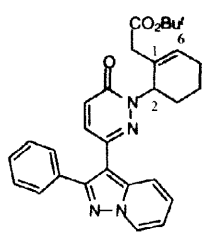


Figure 1. Confomation of cyclohexane ring of **9** and **10**.

On the other hand, the proton at C2 of **9** is in the axial position, since there is lower steric hindrance between the *tert*-butyl ester group and the pyridazinone moiety. It was thus assumed that the structures of **9** and **10** were *exo-Z* and *exo-E* isomer, respectively. Fortunately, crystals of **8**, **9** and **10** suitable for X-ray crystallographic analysis were obtained and results are shown in Figure 2, 3 and 4, respectively.[16] As shown in Figure 3 and 4, the proton at C2 of **10** is present in an equatorial position due to steric hindrance as described above and in **9** is present in the axial position, respectively. The structures of **8**, **9** and **10** were determined in accord with the results of our analysis of NMR. Finally, FR166124 (**1**) was easily obtained in 75% yield by treatment of **7** with TFA in dichloromethane and recrystallization from aqueous ethanol (Scheme 3).



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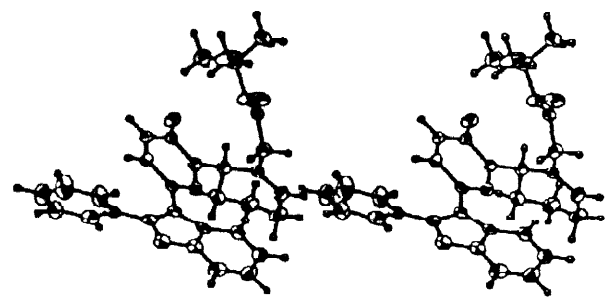
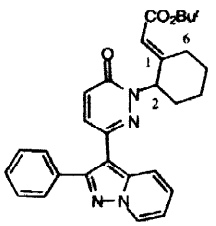


Figure 2. Ortep plot of stereoviews of **8**.



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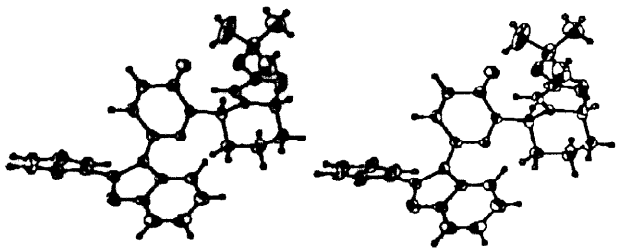
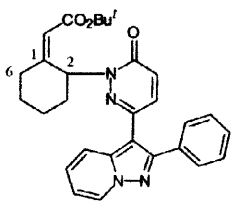


Figure 3. Ortep plot of stereoviews of **9**.



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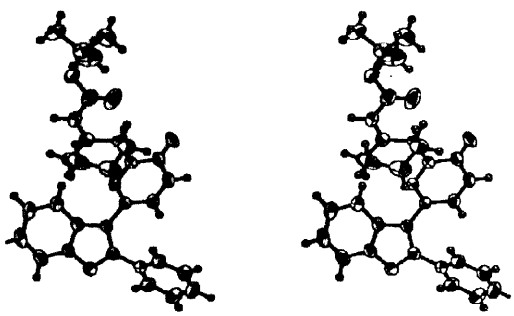
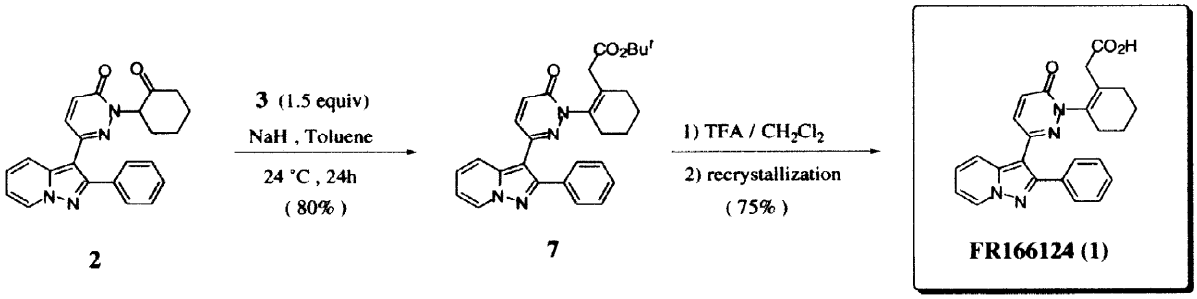


Figure 4. Ortep plot of stereoviews of **10**.

Scheme 3. Synthesis of FR166124 (**1**).



3-3. Mechanism of The Horner–Emmons Reaction and Sequential Isomerization Reaction.

The key reaction in the synthesis of FR166124 was the sequential Horner–Emmons – isomerization reaction of **2** with *tert*-butyl diethylphosphonoacetate using NaH as a base in toluene. Thus, it was important for us to understand the mechanism of this isomerization. In order to understand the mechanism, potential energies of **3**, **7**, **8**, **9** and **10** were assessed by MOPAC PM3 calculation based on the X-ray crystallographical data of **10**. As shown in Figure 5, the *endo* isomers **7** and **8** have lower energy than the *exo* isomers **9** and **10**. For the usual Horner–Emmons products, the *exo-Z* isomer **10** is 0.7 kcal/mol higher in energy than the

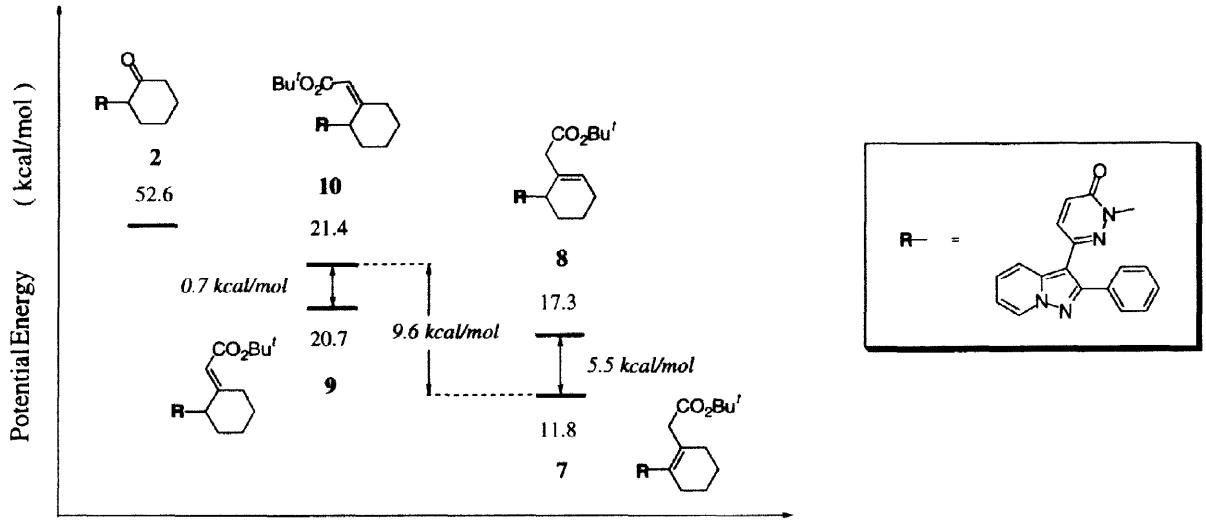


Figure 5. Potential energy diagram of Horner–Emmons products of **2**.

exo-E isomer **9**. Of the unusual Horner–Emmons products, the *endo* isomer **8** is 5.5 kcal/mol higher in energy than **7**. In particular, **7** is 9.6 kcal/mol lower in energy than **10**. Also, from the results shown in Table 2, **8** was obtained as a minor product in up to 1.8% yield. These facts suggested that the *exo* isomers **9** and **10** were formed predominantly as the kinetic products and mainly isomerized to **7** which is the thermodynamically most stable. The remaining features of the isomerization reaction are the isomerization of **10** to **8** and/or **9**, **9** to **7** and/or **8** and **8** to **7**. Therefore, the time-course of this reaction was investigated using HPLC analysis, varying the reaction temperature in the isomerization of these four isomers. Figure 6 and Figure 7 show the time-course of this reaction at 24 °C and 4 to 24 °C respectively, Table 3 shows the isomerization reaction of the *exo-Z* and *E* isomers (**9** and **10**) under thermal and basic conditions. It was observed at 24 °C that **10** was formed rapidly and was changed immediately only to **7** (Figure 6 and Table 3, Entry 11).

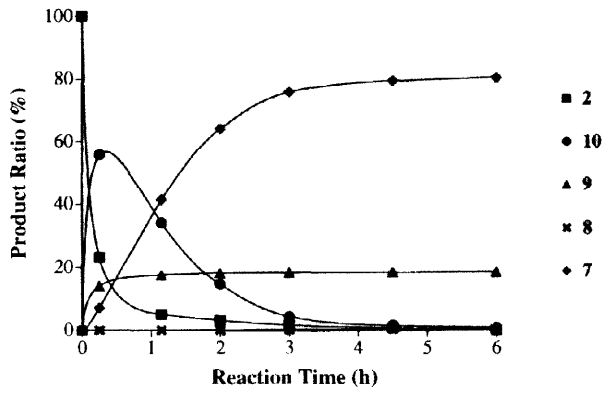


Figure 6
Time-course of Horner–Emmons Reaction at 24 °C.

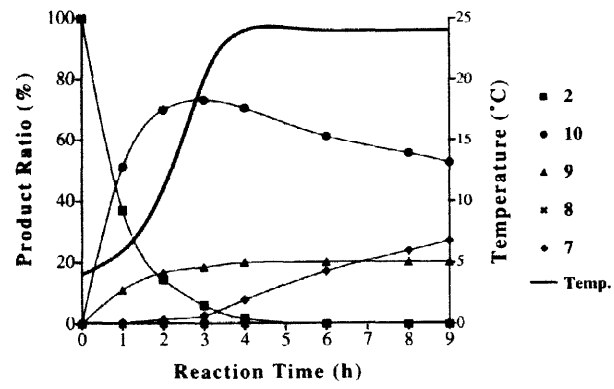


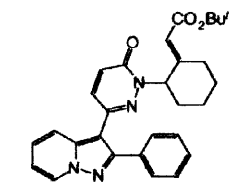
Figure 7
Time-course of Horner–Emmons Reaction at 4 to 24 °C.

It was also found that the isomerization reaction needs temperatures above 15 °C, since **10** was hardly isomerised to **7** below 15 °C (Figure 7). It was also observed that **9** was formed rapidly, but slower than **10**, and was hardly isomerised to **7** and/or other isomers even at 24 °C (Figure 6 and Table 3, Entry 5). As shown in Table 3 (Entries 5, 11) and Table 2 (Entries 4, 5, 6), it was clarified that more than 1.5 equivalents of **3** using NaH as a base were necessary for the key Horner–Emmons reaction and sequential isomerization reaction, despite the fact that **10** could not be isomerised completely to **7** under the conditions of Table 3 (Entry 11). Under thermal conditions, the isomerization reaction was not observed (Table 3, Entries 1, 7), and under DBU conditions, the isomerization reaction needs high temperatures and showed low selectivity (Table 3, Entries 2, 3, 8, 9). As for the basic conditions using NaH, the isomerization reaction showed low selectivity (Table 3, Entries 4, 10).

Table 3

Isomerization Reaction of *exo* Isomers **9** and **10** in toluene for 24 h.

Entry	Conditions	Product ratio [a] (%)			
		7	**8**	**9**	**10**
1	reflux	-----	-----	100	-----
2	1.0 eq. DBU, 24 °C	0.6	0.3	99.1	-----
3	1.0 eq. DBU, reflux	52.0	43.7	4.3	-----
4	1.0 eq. NaH, 24 °C	6.4	2.0	91.6	-----
5	1.0 eq. **3**, 1.0 eq. NaH, 24 °C	1.5	0.3	98.2	-----
6	1.0 eq. **3**, 1.0 eq. *t*-BuOK, 24 °C	57.9	14.7	27.4	-----
7	reflux	-----	-----	-----	100
8	1.0 eq. DBU, 24 °C	0.3	-----	-----	99.7
9	1.0 eq. DBU, reflux	45.6	14.3	2.1	38.0
10	1.0 eq. NaH, 24 °C	22.9	0.4	0.3	76.4
11	1.0 eq. **3**, 1.0 eq. NaH, 24 °C	78.0	-----	-----	22.0
12	1.0 eq. **3**, 1.0 eq. *t*-BuOK, 24 °C	95.8	0.9	1.9	1.4



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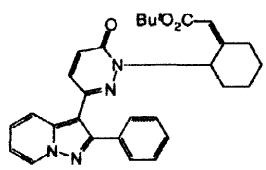

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a : Product ratio was determined by HPLC analysis.

Isomerization of *endo* isomers **7** and **8** were not observed under the conditions of Table 3. From the results described above, it was inferred that deprotonation of the proton at C2 of **10** with the anion of **3** was the critical factor for the isomerization reaction in our Horner–Emmons reaction conditions. Considering the stereo-

electronic effect, it can be presumed that isomerization reaction of **10** proceeds through a change of the conformation from **10** to **10a** and deprotonation of the axial proton at C2 of **10a** (Figure 8). It is considered that change of conformation needs temperature above 15 °C and must proceed slowly, since **10a** is a less stable conformer than **10** as described in Figure 1 and the equilibrium lies so far to **10**. Moreover, it is assumed that isomerization of **8** and **9** needs higher activation energies and higher temperature than **10**, since **8** and **9** were more stable. It was thus concluded that the combination of $(EtO)_2P(O)CH_2CO_2Bu^t$ and NaH as a base was the best reagent for our sequential Horner–Emmons – isomerization reaction.

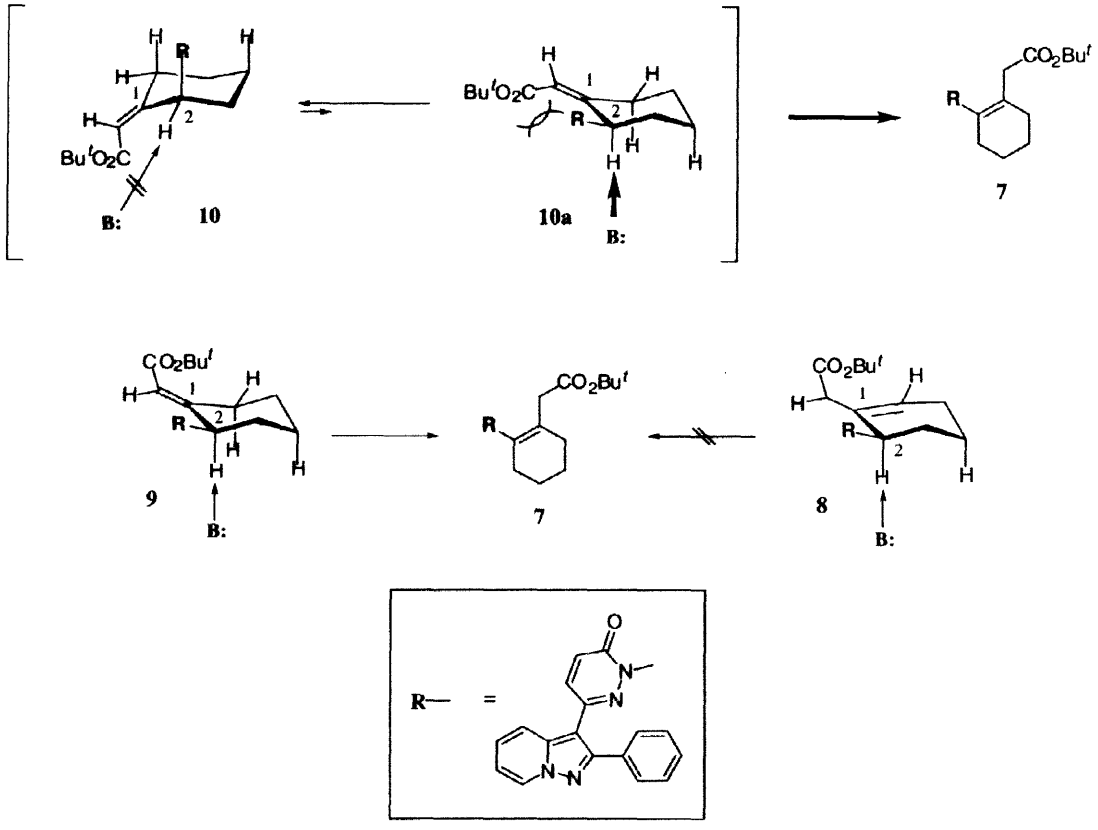

Figure 8. Isomerization process of olefin isomers with the anion of $(EtO)_2P(O)CH_2CO_2Bu^t$ (**B:**).

4. Conclusions

On the basis of results obtained from extensive studies of the sequential Horner–Emmons – isomerization reaction, it has been found that reaction of sterically hindered cyclohexanone **2** with *tert*-butyl diethylphosphonoacetate (**3**) leads to the unusual product **7** and was highly dependent on temperature, base and conformation of the Horner–Emmons products as important factors. Selective synthesis of **7** was thus achieved using this novel sequential Horner–Emmons – isomerization reaction and our sequence provides FR166124 in 42% overall yield from **4**.

5. Experimental

General.

All melting points were determined with a Büchi 535 apparatus in open capillaries and are uncorrected. Infrared (IR) spectra were recorded on a Horiba Spectradesk FT-210 spectrometer as KBr disks. ^{1}H NMR spectra were measured with a Bruker AC200P (200 MHz). Chemical Shifts are given in parts per million (ppm) using tetramethylsilane as the internal standard for spectra obtained in DMSO-d_6 and $CDCl_3$. All J values are given in Hz. Mass (MS) spectra were measured on a Hitachi Model M-1000H mass spectrometer using APCI for ionization. Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyzer. High-performance liquid chromatography (HPLC) was performed using a Hitachi L-4000 equipped with a Waters SYMMETRY^{TM}C$_8$ 4.6 × 150 mm column, eluting with a mixture of H_2O and CH_3CN (1:1) at 1 mL/min flow at room temperature with detection at 254 nm. Column chromatography was performed with the indicated solvents using Merck silica gel 60 (230–400 mesh). Monitoring of reactions was carried out using Merck 60 F_{254} silica gel, glass-supported TLC plates, followed by visualization with UV light (254 and 365 nm) and staining with iodine vapor. Reagents and solvents were used as obtained from commercial suppliers without further purification. Starting 6-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-3(2*H*)-pyridazinone (**4**) was prepared according to the reported method.[10,17] *tert*-Butyl diethylphosphonoacetate (**3**) was prepared from *tert*-butyl bromoacetate and triethyl phosphite according to the reported method.[18]

2-(2-Hydroxycyclohexyl)-6-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-3(2*H*)-pyridazinone (6).

A mixture of **4** (2.0 g, 6.9 mmol), **5** (2.1 mL, 20.9 mmol), sodium hydroxide (320 mg, 8.0 mmol) and benzyltriethylammonium chloride (160 mg, 0.7 mmol) in a mixture of water (20 mL) and toluene (20 mL) was refluxed for 18 h with stirring. The reaction mixture was cooled to room temperature and insoluble solid was collected by filtration. The solid was washed with water and toluene, and dried under reduced pressure to give **6** (2.14 g, 80%) as a solid. Recrystallization afforded an analytical sample. mp 229–231 °C (EtOH–EtOAc); IR (KBr) 3385, 1655, 1585, 1527 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.65 (m, 3H), 1.70–2.30 (m, 5H), 2.42 (d, 1H, J = 7.0 Hz), 3.80–4.10 (m, 1H), 4.94 (td, 1H, J = 10.0, 4.3 Hz), 6.78 (d, 1H, J = 9.6 Hz), 6.91 (t, 1H, J = 7.0 Hz), 7.02 (d, 1H, J = 9.6 Hz), 7.31 (t, 1H, J = 8.0 Hz), 7.42–7.47 (m, 3H), 7.57–7.63 (m, 2H), 7.93 (d, 1H, J = 8.0 Hz), 8.53 (d, 1H, J = 7.0 Hz); MS *m/z* 387 $(M+H)^+$; Anal. Calcd for $C_{23}H_{22}N_4O_3$: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.62; H, 5.71; N, 14.45.

2-(2-Oxocyclohexyl)-6-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-3(2*H*)-pyridazinone (2).

Dimethyl sulfoxide (6.6 mL, 93.0 mmol) was added dropwise to a stirred solution of oxalyl chloride (4.1 mL, 47.0 mmol) in dichloromethane (600 mL) at –70 °C under a nitrogen atmosphere. After 30 minutes, to the reaction mixture was added portionwise **6** (14.9 g, 38.6 mmol) and stirred an additional 30 minutes at –70 °C. After addition of triethylamine (27 mL, 0.193 mol), the reaction mixture was allowed to warm to room temperature. The resulting mixture was poured into water and the organic layer was separated, washed in turn with water, 2 N hydrochloric acid, brine, 5% aqueous sodium hydrogen carbonate and brine, and then dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was crystallized from ethanol to afford **2** (13.0 g, 88%) as a yellow solid. Recrystallization afforded an analytical sample. HPLC Retention

time: 5.3 min; mp 181–182 °C (EtOH); IR (KBr) 1718, 1662, 1587, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.65–2.26 (m, 4H), 2.34–2.73 (m, 4H), 5.79 (dd, 1H, *J* = 11.7, 7.1 Hz), 6.79 (d, 1H, *J* = 9.7 Hz), 6.88 (t, 1H, *J* = 6.9 Hz), 7.03 (d, 1H, *J* = 9.7 Hz), 7.28 (t, 1H, *J* = 6.9 Hz), 7.43–7.48 (m, 3H), 7.61–7.66 (m, 2H), 7.88 (d, 1H, *J* = 6.9 Hz), 8.51 (d, 1H, *J* = 6.9 Hz); MS *m/z* 385 $(M+H)^+$; Anal. Calcd for $C_{23}H_{20}N_4O_3$: C, 71.86; H, 5.24; N, 14.57. Found: C, 71.71; H, 5.12; N, 14.40.

tert-Butyl 2-[6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinyl]-(*E*)-cyclohexylidene-1-acetate (9) and (Z) isomer (10).

To a mixture of potassium *tert*-butoxide (1.7 g, 15.0 mmol) and 18-crown-6-ether (265 mg, 1.0 mmol) in toluene (80 mL) was added dropwise **3** (3.8 g, 15.0 mmol) at 4 °C under a nitrogen atmosphere. After 30 minutes, **2** (3.84 g, 10.0 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature and stirred for 8 h. The resulting mixture was washed in turn with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (toluene–ethyl acetate 10:1) to give **9** (1.0 g, 21%) as the less polar compound (white solid) and **10** (2.35 g, 49%) as the more polar compound (white solid). Recrystallization afforded analytical samples. *Selected data for 9*: R_f = 0.65 (dichloromethane–ethyl acetate 10:1, two-times development); HPLC Retention time: 27.9 min; mp 119–121 °C (toluene); IR (KBr) 1713, 1666, 1593, 1531 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.45–2.50 (m, 7H), 4.00–4.15 (m, 1H), 5.05 (s, 1H), 5.65 (dd, 1H, *J* = 11.8, 3.1 Hz) 6.81 (d, 1H, *J* = 9.6 Hz), 6.86–6.95 (m, 1H), 7.03 (d, 1H, *J* = 9.6 Hz), 7.10–7.65 (m, 6H), 7.89 (d, 1H, *J* = 8.9 Hz), 8.53 (d, 1H, *J* = 6.9 Hz); MS *m/z* 427 $(M-Bu^t+H)^+$, 483 $(M+H)^+$; Anal. Calcd for $C_{29}H_{30}N_4O_3 \cdot 0.67C_6H_5 \cdot CH_3$: C, 74.33; H, 6.55; N, 10.30. Found: C, 74.26; H, 6.49; N, 10.58. *Selected data for 10*: R_f = 0.58 (dichloromethane–ethyl acetate, 10:1 two-times development); HPLC Retention time: 29.8 min; mp 171–172 °C (toluene); IR (KBr) 1701, 1664, 1637, 1593, 1531 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.53–1.93 (m, 4H), 2.23–2.46 (m, 3H), 2.67–2.91 (m, 1H), 5.85 (s, 1H), 6.43 (t, 1H, *J* = 4.2 Hz), 6.79 (d, 1H, *J* = 9.6 Hz), 6.88 (td, 1H, *J* = 9.0, 7.0 Hz), 7.02 (d, 1H, *J* = 9.6 Hz), 7.26 (dd, 1H, *J* = 9.0, 7.0 Hz), 7.41–7.45 (m, 3H), 7.57–7.63 (m, 2H), 7.81 (d, 1H, *J* = 9.0 Hz), 8.51 (d, 1H, *J* = 7.0 Hz); MS *m/z* 427 $(M-Bu^t+H)^+$, 483 $(M+H)^+$; Anal. Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61. Found: C, 71.93; H, 6.51; N, 11.59.

tert-Butyl 2-[6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinyl]-1-cyclohexenylacetate (7) and _tert_-Butyl 6-[6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinyl]-1-cyclohexenylacetate (8).

To a suspension of sodium hydride (60% dispersion in mineral oil, 312 mg, 7.8 mmol) in toluene (40 mL) was added dropwise **7** (2.0 g, 7.8 mmol) at 4 °C under a nitrogen atmosphere. After 30 minutes, **2** (2.0 g, 5.2 mmol) was added to the reaction mixture, which was then allowed to warm to room temperature and stirred for 24 h. The resulting mixture was washed in turn with water and brine, and dried over magnesium sulfate. Evaporation of the solvent gave a residue, which was purified by silica-gel column chromatography (toluene–ethyl acetate 10:1, 5:1 and 2:1) to give **9** (0.4 g, 16%) as the less polar compound (white solid), **8** (40 mg, 1.6%) as a polar compound (white solid) and **7** (2.0 g, 80%) as the more polar compound (yellow amorphous). Recrystallization of **8** afforded an analytical sample; **7** could not be crystallized. *Selected data for 7*: R_f = 0.35 (dichloromethane–ethyl acetate 10:1, two-times development); HPLC Retention time: 17.8 min; IR (KBr) 1728,

1668, 1635, 1593, 1529 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.70–2.00 (m, 4H), 2.00–2.60 (m, 4H), 2.80–3.00 (m, 2H), 6.77 (d, 1H, *J* = 9.7 Hz), 6.85–6.94 (m, 1H), 7.01 (d, 1H, *J* = 9.7 Hz), 7.25–7.35 (m, 1H), 7.40–7.50 (m, 3H), 7.61–7.67 (m, 2H), 8.02 (d, 1H, *J* = 8.9 Hz), 8.51 (d, 1H, *J* = 7.0 Hz); MS *m/z* 427 $(M-Bu^t+H)^+$, 483 $(M+H)^+$. *Selected data for* **8**: R_f = 0.52 (dichloromethane–ethyl acetate 10:1, two-times development); HPLC Retention time: 22.2 min; mp 146–147 °C (ethanol); IR (KBr) 1726, 1668, 1632, 1593, 1524 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.40 (s, 9H), 1.60–2.30 (m, 6H), 2.82 (ABq, 2H, *J* = 15.6, 15.5 Hz), 5.82 (br-s, 1H), 6.06 (br-s, 1H), 6.73 (d, 1H, *J* = 9.7 Hz), 6.85–6.94 (m, 1H), 7.00 (d, 1H, *J* = 9.7 Hz), 7.20–7.65 (m, 6H), 8.07 (d, 1H, *J* = 9.0 Hz), 8.51 (d, 1H, *J* = 6.9 Hz); MS *m/z* 427 $(M-Bu^t+H)^+$, 483 $(M+H)^+$; Anal. Calcd for $C_{29}H_{30}N_4O_3$: C, 72.18; H, 6.27; N, 11.61. Found: C, 72.13; H, 6.51; N, 11.58.

2-[6-Oxo-3-(2-phenylpyrazolo[1,5-*a*]pyridin-3-yl)-1(6*H*)-pyridazinyl]-1-cyclohexenylacetic acid (1) (FR166124).

To a solution of **7** (1.0 g, 2.1 mmol) in dichloromethane (5 mL) was added dropwise trifluoroacetic acid (1.6 mL, 20.7 mmol) at 5 °C under a nitrogen atmosphere. After addition, the reaction mixture was allowed to warm to room temperature and stirred for 20 h. Evaporation of the solvent gave a residue which was azeotroped three times with toluene (15 mL). The resultant residue was partitioned between ethyl acetate and 1 N aqueous sodium hydroxide solution. The aqueous layer was separated, pH was adjusted pH 3.5 with 2 N aqueous hydrochloric acid and extracted with dichloromethane, which was then washed with water and dried over magnesium sulfate. Evaporation of the solvent gave a solid which was recrystallized from 85% aqueous ethanol to give **1** (675 mg, 75%) as a white solid. mp 218–219 °C; IR (KBr) 1722, 1639, 1579, 1531, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.70–2.00 (m, 4H), 2.20–2.70 (m, 4H), 2.91 (d, 1H, *J* = 14.0 Hz), 3.18 (d, 1H, *J* = 14.0 Hz), 6.89–7.00 (m, 2H), 7.17 (d, 1H, *J* = 9.6 Hz), 7.30–7.61 (m, 6H), 7.94 (d, 1H, *J* = 9.0 Hz), 8.55 (d, 1H, *J* = 6.9 Hz), 12.16 (s, 1H); MS *m/z* 427 $(M+H)^+$; Anal. Calcd for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.29; H, 5.21; N, 13.05.

6. X-Ray Crystallographic Analysis.

General.

Diffraction measurements of **8** and **9** were performed on a Rigaku AFC5R diffractometer using graphite monochromatized MoKα radiation (λ = 0.71069 Å). The structures of **8** and **9** were solved by direct methods (SIR88) and refined by a full-matrix least-squares method. Diffraction measurement of **10** was performed on a Rigaku AFC7R diffractometer using graphite monochromatized CuKα radiation (λ = 1.54178 Å). The structure of **10** was solved by direct methods (SHELXS86) and refined by a full-matrix least-squares method.

Compound (8).

Colorless prismatic crystals were grown from ethanol solution. Crystal data: $C_{29}H_{30}O_3N_4$, Mr = 482.58, monoclinic, $P2_1/n$ (#14), a = 13.700 (4) Å, b = 10.224 (3) Å, c = 18.759 (4) Å, β = 105.66 (2)°, V = 2529.9

(9) Å^3, Z = 4, D_{calc} = 1.267 g/cm^3, F(000) = 1024, μ (MoKα) = 0.78 cm^{-1}, T = 296K. A total of 6436 reflections (6186 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 55.1°. The structure was solved using 1842 reflections (I > 3.0 σ(I)). The final refinement converged to R = 0.054 and R_w = 0.055.

Compound (9).

Colorless prismatic crystals were grown from toluene solution. Crystal data: $C_{29}H_{30}O_3N_4$, Mr = 482.58, triclinic, P1 (#2), a = 12.030 (4) Å, b = 12.816 (5) Å, c = 10.674 (4) Å, α = 99.37 (3)°, β = 108.87 (3)°, γ = 69.83 (3)°, V = 1459.3 (10) Å^3, Z = 2, D_{calc} = 1.10 g/cm^3, F(000) = 512, μ (MoKα) = 0.79 cm^{-1}, T = 296K. A total of 7067 reflections (6744 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 55.1°. The structure was solved using 2416 reflections (I > 3.0 σ(I)). The final refinement converged to R = 0.153 and R_w = 0.233.

Compound (10).

Colorless prismatic crystals were grown from toluene solution. Crystal data: $C_{29}H_{30}O_3N_4$, Mr = 482.58, monoclinic, $P2_1/n$ (#14), a = 12.0980 (8) Å, b = 17.3425 (8) Å, c = 12.9941 (7) Å, β = 101.729 (4)°, V = 2669.4 (3) Å^3, Z = 4, D_{calc} = 1.201 g/cm^3, F(000) = 1024, μ (CuKα) = 6.35 cm^{-1}, T = 293K. A total of 4971 reflections (4733 unique reflections) were collected using the ω-2θ scan technique within a 2θ range of 130.2°. The structure was solved using 2442 reflections (I > 2.0 σ(I)). The final refinement converged to R = 0.050 and R_w = 0.037.

Acknowledgments

The authors would like to acknowledge Dr. Hisashi Takasugi and Dr. Kiyoshi Taniguchi for encouragement, Professor Craig A. Merlic, UCLA, for helpful discussions on the isomerization reaction and Dr. David Barrett for helpful discussions and for critical evaluation of this manuscript.

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