An Efficient Synthesis of the Anti-asthmatic Agent T-440: A Selective *N*-Alkylation of 2-Pyridone

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6,7-Diethoxy-1-[1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl]naphthalene-2,3-dimethanol [T-440, (1)] is a potential anti-asthmatic agent based on selective phosphodiesterase 4 inhibition. It was necessary for the further evaluation of 1 to develop an efficient synthetic route for 1, especially the construction of the 1-(2-methoxyethyl)-2-pyridone moiety. We examined an *N*-selective alkylation of pyridone derivative (2) in basic media. 2-Methoxyethylation of 2 with 2-methoxyethyl iodide utilizing LiH as the base gave predominantly an *N*-alkyl pyridone derivative (3a) in 82% yield (*N*/*O*-alkylation=92/8), which is compatible with an *ab initio* calculation of transition-state structures for the methylation of 2-pyridone. Single crystallization of a crude mixture of 3a and 4a furnished pure 3a, which is a key synthetic intermediate of 1.

Key words PDE 4 inhibitor; anti-asthmatic agent; alkylation; pyridone; transition state

Cyclic nucleotide phosphodiesterase 4 (PDE 4) is a key enzyme playing an important role in the hydrolysis of purine cyclic nucleotide, cAMP, to form the respective 5′-mononucleotide. Inhibition of PDE 4 activity results in an increase in cellular levels of cAMP, which has been implicated in the relaxation of airway smooth muscle. Recent interest in this area has focused on the search for selective PDE 4 inhibitors as potential anti-asthmatic agents.[1] We reported 6,7-diethoxy-1-[1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl]naphthalene-2,3-dimethanol, T-440 (**1**, Fig. 1) as a selective and potent PDE 4 inhibitor,[2] and its 1-(2-methoxyethyl)-2-pyridone moiety seems to have a crucial role for PDE 4 inhibitory activity. The regioselective synthesis of the 1-(2-methoxyethyl)-2-pyridone moiety was necessary for the further development of **1**.

Additionally, development of a general method for selective *N*-alkylation of pyridone derivatives would be highly valuable in organic synthesis, since the products would be versatile intermediates for the synthesis of natural products or biologically active compounds.[3] Current synthetic methods of *N*-alkyl-2-pyridone derivatives include selective *N*-alkylation by using alkyl halide in the presence of base[4] or alcohol with diethyl azodicarboxylate and Ph_3P,[5] and the quaternization of pyridine followed by oxidation.[6]

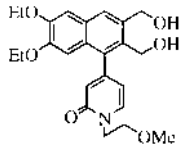

Fig. 1. Structure of T-440 (**1**)

In connection with development of an efficient synthetic route for **1**, we now report studies on construction of the *N*-alkyl-2-pyridone moiety of **1**, which includes the selective *N*-alkylation of **2** using alkyl halide and LiH.

Results and Discussion

In the synthesis of **1**, we obtained the precursor (**3a**) of T-440 by the alkylation of pyridone derivative **2** with 2-methoxyethyl iodide in the presence of NaH as a key reaction.[2] Significant amounts of undesired *O*-alkylated product (**4a**) were also obtained and the isolation of **3a** by silica gel chromatography was necessary for further elaboration. We envisaged that the counter cation (Li, Na, and K) of an ambient anion would play an important role on the *N*/*O* selectivity in this reaction.[3c] In order to evaluate our working hypothe-

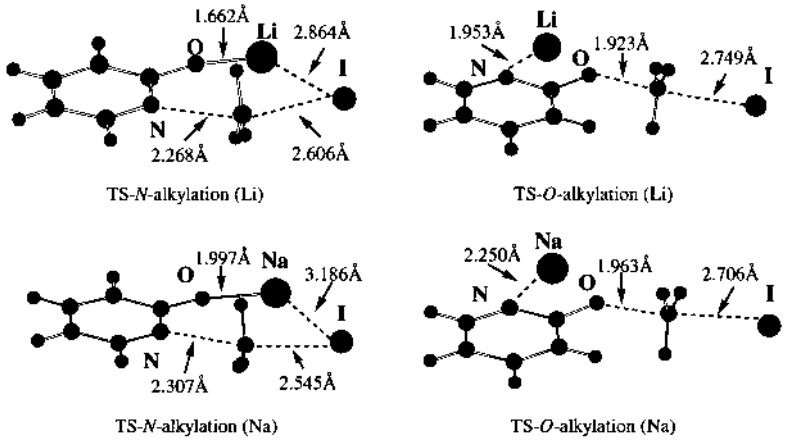

Fig. 2. Transition-State Structures (TS) for *N*- or *O*-Methylation of 2-Pyridone with Li or Na Cation

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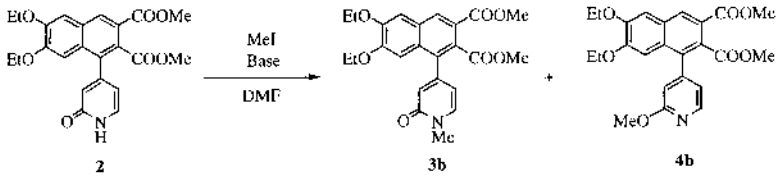
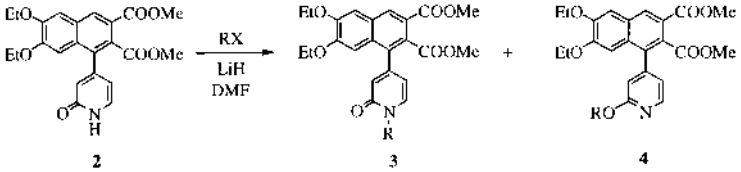
Table 1. Methylation of **2** with Methyl Iodide in the Presence of Various Bases



Run	Base	Ratio (**3b**/**4b**)[a]	Yield (**3b**+**4b**, %)[a]
1	K_2CO_3	97/3	79
2	NaH	98/2	79
3	LiH	>99.9/<0.1	81
4	CsF	93/7	73
5	DBU	96/4	79

a) Ratio (**3b**/**4b**) and yield (**3b**+**4b**) were determined based on the isolated yield of each product (**3b**, **4b**).

Table 2. Alkylation of **2** with Various Alkyl Halides in the Presence of LiH



Entry	RX	Ratio (**3**/**4**)[a]	Yield (**3**+**4**, %)[a]
1	$MeOCH_2CH_2I$ (**a**)	92/8	84
2	MeI (**b**)	>99.9/<0.1	81
3	EtI (**c**)	99/1	85
4	iso-PrI (**d**)	83/17	28[b]
5	Benzyl bromide (**e**)	>99.9/<0.1	82
6	Allyl bromide (**f**)	95/5	80

a) Ratio (**3**/**4**) and yield (**3**+**4**) were determined based on the isolated yield of each product (**3**, **4**). *b*) Starting material was recovered in 47%.

sis, we carried out *ab initio* calculations of transition-state structures for the methylation of 2-pyridone as a model study at the HF/3-21G level using GAUSSIAN 94.[7] The energy difference between transition-state structures of *N*-methylation and *O*-methylation using Li metal was 5.45 kcal/mol, whereas for Na metal it was 4.09 kcal/mol (Fig. 2). From these results, *N*-methyl-2-pyridone was estimated to be obtained predominantly by using the Li cation instead of the Na cation.

In order to experimentally confirm the effects of the counter cation on *N*/*O* selectivity, we tried methylation of **2** with MeI in the presence of K_2CO_3, NaH, LiH, CsF, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in *N*,*N*-dimethylformamide (DMF); the ratios were determined on the basis of the isolated yield of each product by silica gel chromatography. The selectivity of *N*-methylation is in fair agreement with the estimation from energy calculation, and LiH gave the best *N*-selectivity among the various bases (Table 1).

Based on these results, we next examined the alkylation of **2** with a variety of alkyl halides, including 2-methoxyethyl iodide, using LiH as the base (Table 2). **2** was treated with alkyl halide and LiH in DMF at 50 °C for 20 h to afford a mixture of **3** and **4** in good to excellent selectivity in high yield, except for isopropyl iodide that gave a lower yield probably because of steric hindrance; the *N*/*O* ratio was determined on the basis of the isolated yield of each product by silica gel chromatography. Moreover, we found that pure **3a**

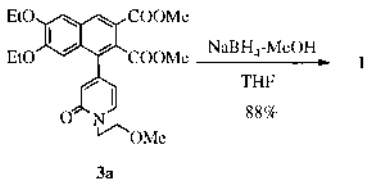


Chart 1. Reduction of **3a** to T-440 (**1**)

could be obtained in 70% yield without difficulty by a single crystallization of the crude mixture (**3a**/**4a**=92/8) from AcOEt. Reduction of **3a** by treatment with $NaBH_4$ and MeOH in refluxing tetrahydrofuran (THF)[8] gave T-440 (**1**) in 88% yield (Chart 1).

In conclusion, we have achieved the selective *N*-alkylation of pyridone derivative **2**, which has enabled the large-scale synthesis of the anti-asthmatic agent T-440 (**1**). In the reaction, we found that the selectivity of *N*-alkylation increases in order of Na and Li metal, which is compatible with the results of *ab initio* calculations in the model study.

Experimental

Melting points were determined on a Büchi 545 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II analyzer. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H-NMR spectra were obtained on a Bruker AC-200 (200 MHz) spectrometer with Me_4Si as an internal standard. Mass spectra were obtained on a Hitachi M-2000A double-focusing mass spectrometer. Column chromatography was performed with silica gel (E. Merck, 70—230 mesh). Reactions were monitored by TLC using 0.25 mm silica gel

F254 (E. Merck) glass plates.

General Procedure for the Alkylation of Pyridones (2) Base (1.2 mmol) was added to a solution of **2** (1.0 mmol) in DMF (5 ml), and the mixture was stirred at 50 °C for 2 h under nitrogen atmosphere. Alkyl halide (1.5 mmol) was added, and the mixture was stirred overnight at 50 °C. After being allowed to cool to room temperature, the reaction mixture was poured into a mixture of aqueous $NaHCO_3$ and AcOEt, and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the residue by chromatography gave **3** and **4**. All purified compounds were characterized as follows:

6,7-Diethoxy-1-[1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl]naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3a) mp 101—103 °C. IR (KBr) cm^{-1}: 1724, 1660, 1250, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.36 (3H, s), 3.68—3.83 (2H, m), 3.75 (3H, s), 3.93 (3H, s), 3.93—4.12 (2H, m), 4.12—4.31 (4H, m), 6.17 (1H, dd, J=6.9, 1.9 Hz), 6.59 (1H, d, J=1.9 Hz), 6.91 (1H, s), 7.23 (1H, s), 7.44 (1H, d, J=6.9 Hz), 8.42 (1H, s). EIMS *m/z*: 483 (M^+), 425 (base). *Anal*. Calcd for $C_{26}H_{29}NO_8$: C, 64.59; H, 6.05; N, 2.90. Found: C, 64.30; H, 5.90; N, 2.61.

6,7-Diethoxy-1-[2-(2-methoxyethyl)oxypyridin-4-yl]naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (4a) mp 128—130 °C. IR (KBr) cm^{-1}: 1723, 1251, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.46 (3H, s), 3.65 (3H, s), 3.79 (2H, t, J=5.0 Hz), 3.82—4.05 (2H, m), 3.93 (3H, s), 4.23 (2H, q, J=7.0 Hz), 4.45—4.62 (2H, m), 6.73 (1H, s), 6.83 (1H, dd, J=1.4, 0.7 Hz), 6.89 (1H, dd, J=5.2, 1.4 Hz), 7.23 (1H, s), 8.23 (1H, dd, J=5.2, 0.7 Hz), 8.44 (1H, s). EIMS *m/z*: 483 (M^+), 424 (base). *Anal*. Calcd for $C_{26}H_{29}NO_8$: C, 64.59; H, 6.05; N, 2.90. Found: C, 64.33; H, 5.81; N, 2.63.

6,7-Diethoxy-1-(1-methyl-2-oxo-1,2-dihydropyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3b) mp 190—191 °C. IR (KBr) cm^{-1}: 1725, 1662, 1248, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.64 (3H, s), 3.77 (3H, s), 3.93 (3H, s), 3.92—4.15 (2H, m), 4.24 (2H, q, J=7.0 Hz), 6.20 (1H, dd, J=6.9, 1.9 Hz), 6.61 (1H, d, J=1.9 Hz), 6.89 (1H, s), 7.23 (1H, s), 7.37 (1H, d, J=6.9 Hz), 8.42 (1H, s). EIMS *m/z*: 438 (M^+-1, base). *Anal.* Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.45; H, 5.45; N, 2.99.

6,7-Diethoxy-1-(2-methyloxypyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (4b) mp 67—69 °C. IR (KBr) cm^{-1}: 1724, 1250, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.66 (3H, s), 3.94 (3H, s), 4.01 (3H, s), 3.83—4.08 (2H, m), 4.24 (2H, q, J=7.0 Hz), 6.75 (1H, s), 6.77 (1H, d, J=1.4 Hz), 6.89 (1H, dd, J=5.2, 1.4 Hz), 7.23 (1H, s), 8.27 (1H, d, J=5.2 Hz), 8.44 (1H, s). EIMS *m/z*: 439 (M^+, base). *Anal*. Calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19. Found: C, 65.29; H, 5.64; N, 2.94.

6,7-Diethoxy-1-(1-ethyl-2-oxo-1,2-dihydropyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3c) mp 163—164 °C. IR (KBr) cm^{-1}: 1728, 1661, 1251, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (3H, t, J=7.2 Hz), 1.46 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.76 (3H, s), 3.93 (3H, s), 3.93—4.17 (4H, m), 4.23 (2H, q, J=7.0 Hz), 6.21 (1H, dd, J=6.9, 1.9 Hz), 6.59 (1H, d, J=1.9 Hz), 6.90 (1H, s), 7.23 (1H, s), 7.36 (1H, d, J=6.9 Hz), 8.42 (1H, s). EIMS *m/z*: 452 (M^+-1, base). *Anal*. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 65.98; H, 5.85; N, 2.98.

6,7-Diethoxy-1-(2-ethyloxypyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (4c) mp 124—125 °C. IR (KBr) cm^{-1}: 1725, 1251, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 1.43 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.66 (3H, s), 3.94 (3H, s), 3.95 (2H, q, J=7.0 Hz), 4.24 (2H, q, J=7.0 Hz), 4.41 (2H, q, J=7.0 Hz), 6.70—6.80 (2H, m), 6.87 (1H, dd, J=5.2, 1.4 Hz), 7.23 (1H, s), 8.24 (1H, dd, J=5.2, 0.6 Hz), 8.44 (1H, s). EIMS *m/z*: 453 (M^+, base). *Anal*. Calcd for $C_{25}H_{27}NO_7$: C, 66.21; H, 6.00; N, 3.09. Found: C, 66.20; H, 6.00; N, 2.92.

6,7-Diethoxy-1-(1-isopropyl-2-oxo-1,2-dihydropyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3d) mp 152—153 °C. IR (KBr) cm^{-1}: 1731, 1656, 1256, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.35—1.50 (9H, m), 1.55 (3H, t, J=7.0 Hz), 3.74 (3H, s), 3.93 (3H, s), 3.92—4.11 (2H, m), 4.24 (2H, q, J=7.0 Hz), 5.35 (1H, septet, J=6.8 Hz), 6.25 (1H, dd, J=7.0, 1.9 Hz), 6.59 (1H, d, J=1.9 Hz), 6.91 (1H, s), 7.23 (1H, s), 7.42 (1H, d, J=7.0 Hz), 8.42 (1H, s). EIMS *m/z*: 466 (M^+-1, base). *Anal*. Calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.25; N, 3.00. Found: C, 66.78; H, 6.00; N, 2.89.

6,7-Diethoxy-1-(2-isopropyloxypyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (4d) mp 147—148 °C. IR (KBr) cm^{-1}: 1724, 1250, 1125. ^{1}H-NMR ($CDCl_3$) δ: 1.30—1.49 (9H, m), 1.55 (3H, t, J=7.0 Hz), 3.65 (3H, s), 3.94 (3H, s), 3.96 (2H, q, J=7.0 Hz), 4.24 (2H, q, J=7.0 Hz), 5.34 (1H, septet, J=6.2 Hz), 6.70 (1H, d, J=1.4 Hz), 6.78 (1H, s), 6.84 (1H, dd, J=5.2, 1.4 Hz), 7.23 (1H, s), 8.24 (1H, d, J=5.2 Hz), 8.43 (1H, s). EIMS *m/z*: 467 (M^+, base). *Anal*. Calcd for $C_{26}H_{29}NO_7$: C, 66.80; H, 6.25; N, 3.00. Found: C, 66.61; H, 6.11; N, 2.80.

6,7-Diethoxy-1-(1-benzyl-2-oxo-1,2-dihydropyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3e) mp 160—161 °C. IR (KBr) cm^{-1}: 1719, 1662, 1251, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.44 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.73 (3H, s), 3.93 (3H, s), 4.02 (2H, qd, J=7.0, 2.2 Hz), 4.23 (2H, q, J=7.0 Hz), 5.25 (2H, s), 6.18 (1H, dd, J=6.9, 1.9 Hz), 6.65 (1H, d, J=1.9 Hz), 6.88 (1H, s), 7.22 (1H, s), 7.22—7.45 (6H, m), 8.42 (1H, s). EIMS *m/z*: 515 (M^+, base). *Anal*. Calcd for $C_{30}H_{29}NO_7$: C, 69.89; H, 5.67; N, 2.72. Found: C, 69.80; H, 5.92; N, 2.56.

6,7-Diethoxy-1-(1-allyl-2-oxo-1,2-dihydropyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (3f) mp 135—136 °C. IR (KBr) cm^{-1}: 1724, 1663, 1251, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.76 (3H, s), 3.94 (3H, s), 3.93—4.15 (2H, m), 4.24 (2H, q, J=7.0 Hz), 4.67 (2H, dd, J=5.6, 1.5 Hz), 5.23 (1H, dd, J=17.0, 1.2 Hz), 5.34 (1H, dd, J=10.2, 1.2 Hz), 6.06 (1H, ddt, J=17.0, 10.2, 5.6 Hz), 6.22 (1H, dd, J=6.9, 1.9 Hz), 6.62 (1H, d, J=1.4 Hz), 6.90 (1H, s), 7.23 (1H, s), 7.34 (1H, d, J=6.9 Hz), 8.43 (1H, s). EIMS *m/z*: 465 (M^+, base). *Anal*. Calcd for $C_{26}H_{27}NO_7$: C, 67.09; H, 5.85; N, 3.01. Found: C, 67.04; H, 5.91; N, 2.97.

6,7-Diethoxy-1-(2-allyloxypyridin-4-yl)naphthalene-2,3-dicarboxylic Acid Dimethyl Ester (4f) mp 108—110 °C. IR (KBr) cm^{-1}: 1720, 1252, 1126. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (3H, t, J=7.0 Hz), 1.55 (3H, t, J=7.0 Hz), 3.66 (3H, s), 3.94 (3H, s), 3.95 (2H, q, J=7.0 Hz), 4.24 (2H, q, J=7.0 Hz), 4.91 (2H, dd, J=5.4, 1.5 Hz), 5.27 (1H, dd, J=10.4, 1.4 Hz), 5.42 (2H, dd, J=17.2, 1.6 Hz), 6.12 (1H, ddt, J=17.2, 10.4, 5.4 Hz), 6.75 (1H, s), 6.80 (1H, dd, J=1.4, 0.7 Hz), 6.89 (1H, dd, J=5.2, 1.4 Hz), 7.23 (1H, s), 8.25 (1H, dd, J=5.2, 0.7 Hz), 8.44 (1H, s). EIMS *m/z*: 465 (M^+, base). *Anal*. Calcd for $C_{26}H_{27}NO_7$: C, 67.09; H, 5.85; N, 3.01. Found: C, 66.91 H, 5.90; N, 2.95.

6,7-Diethoxy-1-[1-(2-methoxyethyl)-2-oxo-1,2-dihydropyridin-4-yl]naphthalene-2,3-dimethanol T-440 (1) To a stirred suspension of **3a** (4.3 g, 8.9 mmol) and $NaBH_4$ (3.4 g, 89.0 mmol) in THF (60 ml) was added MeOH (15 ml) dropwise under reflux over 1 h, and the mixture was stirred under reflux for another 1 h. The reaction mixture was allowed to cool to room temperature and concentrated under reduced pressure. The residue was poured into a mixture of 10% aqueous HCl (75 ml) and $CHCl_3$ (150 ml), and the organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Crystallization of the residue from AcOEt–hexane gave **1** (3.3 g, 88%), mp 130—131 °C. IR (KBr) cm^{-1}: 3387, 1656. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, t, J=7.0 Hz), 1.53 (3H, t, J=7.0 Hz), 3.35 (3H, s), 3.72 (2H, t, J=5.0 Hz), 3.82—4.03 (2H, m), 4.03—4.35 (4H, m), 4.35—4.70 (2H, m), 4.70—5.00 (2H, m), 6.10 (1H, dd, J=6.8, 1.8 Hz), 6.46 (1H, d, J=1.8 Hz), 6.65 (1H, s), 7.02 (1H, s), 7.43 (1H, d, J=6.8 Hz), 7.62 (1H, s). EIMS *m/z*: 427 (M^+), 351 (base). *Anal*. Calcd for $C_{24}H_{29}NO_6$: C, 67.43; H, 6.84; N, 3.28. Found: C, 67.01; H, 6.66; N, 2.84.

References and Notes

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