Total Synthesis of Maturinone through a Regioselective Diels–Alder Reaction of 5-Brominated Benzofurandione

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Maturinone was efficiently prepared by means of a regiocontrolled Diels–Alder reaction between 5-bromo-2-ethoxycarbonyl-3-methylbenzo[*b*]furan-4,7-dione 8 and penta-1,3-diene.

Key words maturinone; Diels–Alder reaction; bromobenzofurandione

The Diels–Alder cyclization between appropriate dienes and quinones is one of the most powerful reactions for the construction of polycyclic quinonoid compounds. However, unsymmetrical dienes and dienophiles often afford mixtures of regioisomers that are not easily separable. In efforts to elaborate regiocontrolled methodologies, a new strategy, based on the blocking effect of a bromine atom located on the double bond of the quinone, has recently received attention.[1,2] We applied this methodology to the regiospecific synthesis of azaanthraquinones and furoquinoline-4,9-diones.[3-5] In this paper, we wish to report its application in the total synthesis of maturinone **1**, a naturally occurring naphthofurandione.

Results and Discussion

Compound **1** was first obtained by semisynthesis in 1966.[6] A few months later, it was isolated from *Cacalia decomposita* A. GRAY, a plant from northern Mexico,[7] used in the treatment of diabetes.[8] Maturinone **1** has since been found in numerous other vegetable extracts.[9-14] Its total synthesis has been achieved *via* several pathways, but their interest is limited owing to poor overall yields.[15-18] Among them, the Diels–Alder reaction between 3-methylbenzofuran-4,7-dione and penta-1,3-diene was the most direct, but the reaction favors the unnatural regioisomer (isomaturinone).[19] Regiocontrol of the [4+2] cycloaddition was then envisaged through the preparation and use of a 5-brominated benzofurandione (Chart 1).

We thought the quinone **2** would be easily accessible by oxidation of the phenolic precursor **3**. But, bromination of **4**, using bromine in chloroform, gave an inseparable mixture of products, of which one was brominated at C-2. Thus, protection of this position appeared necessary. We decided to start with the phenolic derivative **5** containing an ethoxycarbonyl group, which would be easily removable in the final step[20] (Chart 2).

Oxidation of **6**[21] with Frémy's salt was inefficient. The starting material was not totally consumed, even in the presence of a large excess of the oxidizing agent. On the other hand, the use of bis(trifluoroacetoxy)iodobenzene gave **8** in poor yield. For these reasons, we turned our attention to the dibromophenol **7**,[21] since *para*-brominated phenolic derivatives were successfully oxidized to *para*-quinones with chromic anhydride.[22,23] Compound **7** was obtained in 86% yield by using a modification of the literature procedure.[21] Oxidation with chromic anhydride then gave the desired quinone **8** in 63% yield. The [4+2] cycloaddition between **8** and penta-1,3-diene (Chart 3) was performed in the presence of sodium bicarbonate.[4,5] This base was used in order to trap hydrogen bromide evolved and to avoid polymerization of the penta-1,3-diene.

As expected, the cycloaddition was totally regioselective: the nucleophilic end of the diene exclusively attacks the unbrominated carbon C-6 of the quinone **8**. The primary adduct of the reaction was not observed, but we isolated the dihydro derivative **9** in a good yield. Deprotection of C-2 was performed by alkaline hydrolysis of the ethoxycarbonyl group followed by a high-temperature decarboxylation using copper powder in quinoline. Physical and spectroscopical data of the final compound were identical with those of a sample of maturinone **1** obtained according

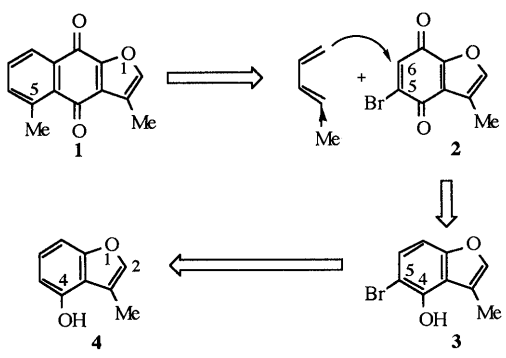

Chart 1

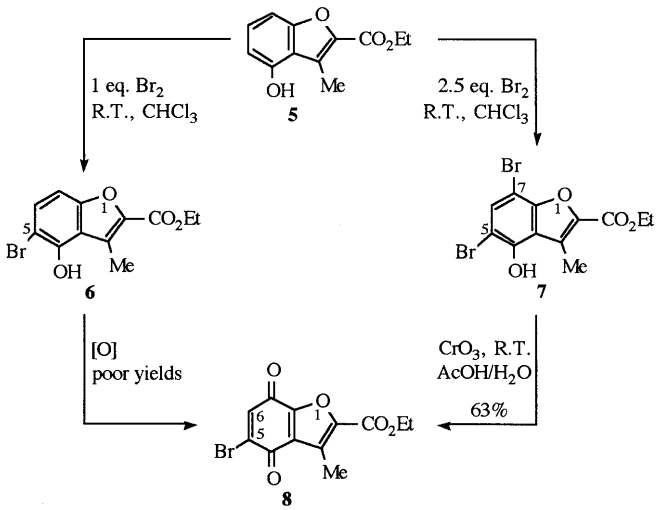

Chart 2

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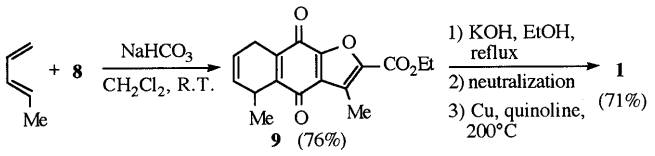

Chart 3

to the procedure described by Kakisawa and Inouye.[19] The overall yield was 16% calculated from commercially available materials (cyclohexane-1,3-dione and ethyl 2-chloroacetoacetate).

Conclusion

We have provided an efficient access to maturinone **1** using a regiocontrolled Diels–Alder strategy from a 5-brominated benzofurandione. This result illustrates the potential of this methodology for regioselective total synthesis of natural quinonoid products.

Experimental

Melting points were taken in a capillary tube with a Buchi 510 apparatus without correction. IR spectra were recorded on a Perkin-Elmer 1310 apparatus. ^{1}H-NMR spectra were obtained on a Bruker AM 300 spectrometer using Me_4Si as an internal standard. Coupling constant (J) values are given in Hz. TLC analyses were performed on silica gel (Merck) F-254 aluminium sheets. Matrex 60 Å (35—70 μm) silica gel was used for column chromatography. Circular preparative thin layer chromatography (Harrison Research Chromatotron 8924) was done with Merck silica gel containing gypsum.

4-Hydroxybenzofuran **5** was prepared from cyclohexane-1,3-dione and ethyl 2-chloroacetoacetate according to the procedures described in the literature.[24,25]

5,7-Dibromo-2-ethoxycarbonyl-4-hydroxy-3-methylbenzo[*b*]furan (7)[21] A solution of bromine (2 g, 12.51 mmol) in $CHCl_3$ (15 ml) was added dropwise to a solution of compound **5** (1.09 g, 4.95 mmol) in $CHCl_3$ (50 ml) at room temperature. At the end of the addition, stirring was continued for 1 h. After evaporation of the solvent, the white solid obtained was recrystallized from MeOH to yield **7** (1.61 g, 86%, lit.[21] 72%). mp 172 °C. IR (KBr): 3360, 1710, 1600 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.64 (1H, s, 6-H), 5.92 (1H, s, OH), 4.46 (2H, q, J=7.1, CH_2–CH_3), 2.74 (3H, s, 3-CH_3), 1.45 (3H, t, J=7.1, CH_2–CH_3).

5-Bromo-2-ethoxycarbonyl-3-methylbenzo[*b*]furan-4,7-dione (8) A solution of CrO_3 (0.15 g, 1.5 mmol) in water (1 ml) was added dropwise to a solution of compound **7** (0.189 g, 0.5 mmol) in 4.5 ml of a mixture of CH_3CO_2H/H_2O (3.5/1) at room temperature. At the end of the addition, stirring was continued for 1 h. The final reaction mixture was then diluted with 40 ml of water and extracted with Et_2O (3 × 25 ml). The organic layer was washed with water until the pH of the washing became neutral, dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography (hexane/EtOAc: 85/15 as the eluent). The yellow solid obtained was recrystallized from hexane/EtOAc (90/10) to yield **8** (0.1 g, 63%). mp 152 °C. IR (KBr): 1710, 1685, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 7.31 (1H, s, 6-H), 4.43 (2H, q, J=7.1, CH_2–CH_3), 2.63 (3H, s, 3-CH_3), 1.41 (3H, t, J=7.1, CH_2–CH_3), *Anal.* Calcd for $C_{12}H_9BrO_5$: C, 46.03; H, 2.90; Br, 25.52. Found: C, 46.03; H, 2.92; Br, 25.46.

2-Ethoxycarbonyl-5,8-dihydro-3,5-dimethylnaphtho[2,3-*b*]furan-4,9-dione (9) Penta-1,3-diene (0.681 g, 10 mmol) was rapidly added to a mixture of the quinone **8** (0.316 g, 1.01 mmol) and $NaHCO_3$ (0.252 g, 3 mmol) in CH_2Cl_2 (6 ml) at room temperature. At the end of the addition, stirring was continued for 24 h. The final reaction mixture was then diluted with 20 ml of CH_2Cl_2 and filtered. After evaporation of the solvent, the residue was purified by circular preparative thin layer chromatography with hexane/EtOAc (90/10). The yellow solid obtained was recrystallized from MeOH to yield **9** (0.23 g, 76%). mp 155 °C. IR (KBr): 1720, 1685, 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 5.87—5.77 (2H, m, 6-H, 7-H), 4.42 (2H, q, J=7.1, CH_2–CH_3), 3.56—3.51 (1H, m, 5-H), 3.34—2.97 (2H, m, 8-H), 2.62 (3H, s, 3-CH_3), 1.41 (3H, t, J=7.1, CH_2–CH_3), 1.21 (3H, d, J=6.9, 5-CH_3). *Anal.* Calcd for $C_{17}H_{16}O_5$: C, 67.99; H, 5.36. Found: C, 67.76; H, 5.31.

3,5-Dimethylnaphtho[2,3-*b*]furan-4,9-dione (1) (Maturinone) A mixture of compound **9** (0.05 g, 0.17 mmol) and KOH (0.029 g, 3 mmol) in EtOH (2 ml) was maintained at reflux for 1 h. After having cooled to room temperature, this solution was neutralized with concentrated HCl. The precipitate was collected and dissolved in Et_2O (15 ml). This solution was washed with water, dried over anhydrous Na_2SO_4 and evaporated under vacuum. Then, quinoline (1.5 ml) and copper powder (0.019 g, 0.29 mmol) were added to the residue. The resulting mixture was heated at 200 °C for 45 min, then cooled at room temperature, diluted with Et_2O (20 ml) and filtered. The filtrate was washed with a 10% aqueous solution of HCl (3 × 10 ml) and then with water until the pH of the washing was neutral. It was dried over anhydrous Na_2SO_4 and evaporated, and the residue was purified by circular preparative thin layer chromatography with hexane/EtOAc (80/20). The yellow solid thus obtained was recrystallized from EtOH to yield maturinone **1** (0.027 g, 71%). mp 164 °C (lit.,[19] mp 164—166 °C). IR (KBr): 1670 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 8.16 (1H, dd, J=7.5, 1.5, 8-H), 7.60 (1H, dd, J=7.5, 7-H), 7.53—7.51 (2H, m, 6-H, 2-H), 2.81 (3H, s, 5-CH_3), 2.38 (3H, d, J=1.1, 3-CH_3). ^{1}H-NMR (C_6D_6) δ: 8.20 (1H, dd, J=7.5, 1.4, 8-H), 6.98 (1H, dd, J=7.5, 7-H), 6.91 (1H, dd, J=7.5, 1.4, 6-H), 6.58 (1H, q, J=1.1, 2-H), 2.72 (3H, s, 5-CH_3), 2.05 (3H, d, J=1.1, 3-CH_3).

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References

1) Grunwell J. R., Karipides A., Wigal C. T., Heinzman S. W., Parlow J., Surso J. A., Clayton L., Fleitz F. J., Daffner M., Stevens J. E., *J. Org. Chem.*, **56**, 91—95 (1991) and references cited therein.
2) Krohn K., Khanbabaee K., *Justus Liebigs Ann. Chem.*, **1994**, 1109—1112.
3) Bouammali B., Pautet F., Fillion H., Soufiaoui M., *Tetrahedron*, **49**, 3125—3130 (1993).
4) Chaker L., Pautet F., Fillion H., *Heterocycles*, **41**, 1169—1179 (1995).
5) Cherkaoui O., Nebois P., Fillion H., Domard M., Fenet B., *Tetrahedron*, **52**, 9499—9508 (1996).
6) Joseph-Nathan P., Morales J. J., Romo J., *Tetrahedron*, **22**, 301—307 (1966).
7) Correa J., Romo J., *Tetrahedron*, **22**, 685—691 (1966).
8) Romo J., Joseph-Nathan P., *Tetrahedron*, **20**, 2331—2337 (1964).
9) Naya K., Miyoshi Y., Mori H., Takai K., Nakanishi M., *Chem. Lett.*, **1976**, 73—76.
10) Joshi K. C., Singh P., Singh G., *Indian J. Chem.*, **14B**, 637—638 (1976).
11) El-Emary N. A., Takemoto T., Kusano G., *Planta Med.*, **38**, 161—164 (1980).
12) Torres P., Mancheno B., Chinchilla R., Asensi M. C., Grande M., *Planta Med.*, **54**, 257—258 (1988).
13) Torres P., Chinchilla R., Asensi M. C., Grande M., *Phytochemistry*, **28**, 3093—3095 (1989).
14) Abdo S., De Bernardi M., Marinoni G., Mellerio G., Samaniego S., Vidari G., Vita Finzi P., *Phytochemistry*, **31**, 3937—3941 (1992).
15) Brown P. M., Thomson R. H., *J. Chem. Soc.*, (*C*), **1969**, 1184—1186.
16) Ruiz R. M., Correa J., Maldonado L. A., *Bull. Soc. Chim. Fr.*, **1969**, 3612—3614.
17) Inouye Y., Uchida Y., Kakisawa H., *Bull. Chem. Soc. Jpn.*, **50**, 961—966 (1977).
18) Kobayashi K., Shimizu H., Sasaki A., Suginome H., *J. Org. Chem.*, **58**, 4614—4618 (1993).
19) Kakisawa H., Inouye Y., *Tetrahedron Lett.*, **1969**, 1929—1932.
20) Salvi V. S., Sethna S., *J. Indian Chem. Soc.*, **44**, 135—139 (1967).
21) Grinev A. N., Lyubchanskaya V. M., Uretskaya G. Y., *Khim. Geterotsikl. Soedin*, **1**, 27—29 (1980) [*Chem. Abst.*, **93**, 26184*h* (1980)].
22) Abd El Rahman A. H., Basha R. M., *Z. Naturforsh. B. Anorg. Chem., Org. Chem.*, **32B**, 1084—1088 (1977).
23) Botha M. E., Giles R. G. F., Yorke S. C., *J. Chem. Soc., Perkin Trans. 1*, **1991**, 85—88.
24) Stetter H., Lauterbach R., *Chem. Ber.*, **93**, 603—607 (1960).
25) Demerseman P., Lechartier J.-P., Pene C., Cheutin A., Royer R., *Bull. Soc. Chim. Fr.*, **1965**, 1473—1486.