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A NOVEL DIELS-ALDER REACTION UTILIZING 3-CHLORO-1-METHOXYBUTADIENE:

A SHORT AND CONVERGENT SYNTHESIS OF THE 5-LIPOXYGENASE INHIBITOR RS-43179

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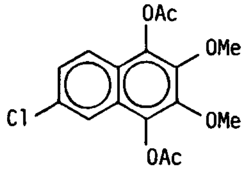
Abstract: Diels-Alder reaction of 3-chloro-1-methoxy-1,3-butadiene (1) with 2,3-dimethoxy-2,5-cyclohexadiene-1,4-dione (2) provides a facile and convergent synthesis of the β-halogenated polysubstituted naphthalene 5-lipoxygenase inhibitor RS-43179.

During the course of our investigations in the area of leukotriene modulation, we had need of gram quantities of the compound RS-43179, a selective 5-lipoxygenase inhibitor currently in Phase II clinical trials for the treatment of psoriasis.[1]

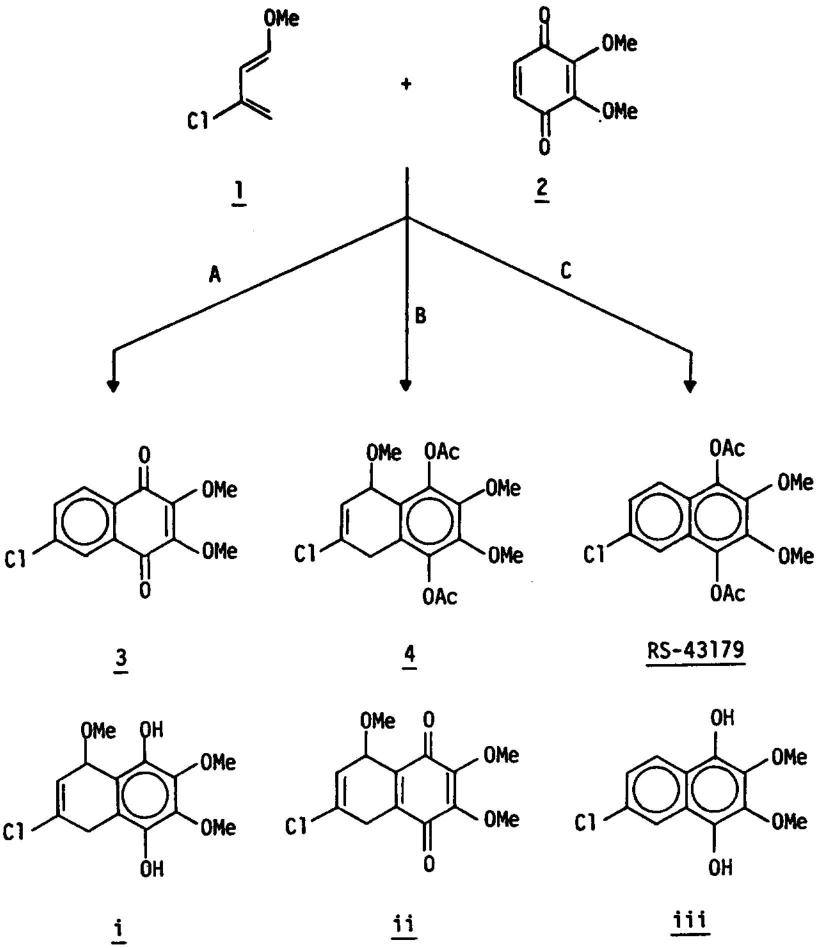


RS-43179

Rather than utilize the lengthy procedure patented for the preparation RS-43179[2,3] we undertook a short and convergent approach to beta-halogenated polysubstituted naphthalene derivatives which has culminated in a one-pot preparation of RS-43179 from known and readily available starting materials. Our strategem was based on the proposed Diels-Alder reaction between 3-chloro-1-methoxy-1,3-butadiene (1)[4] and 2,3-dimethoxy-2,5-cyclohexadiene-1,4-dione (2).[5] Interestingly, as far as we know, 3-chloro-1-methoxy-1,3-butadiene has never been reported in Diels-Alder chemistry.

We found that the Diels-Alder products isolated from the reaction of 1 and 2 varied depending on the reaction sequence employed (Scheme). Reaction of the quinone 2 with 3-chloro-1-methoxy-1,3-butadiene (1) at RT under an inert atmosphere,[6] followed by briefly bubbling air through the reaction mixture (Scheme, pathway A) afforded 6-chloro-2,3-dimethoxy-1,4-naphthalenedione 3 in 72% yield. Compounds i and ii are presumed to be intermediates in the reaction vessel en route to 3.

SCHEME



Reaction of the quinone 2 with 1 at RT under inert atmosphere as above, followed by trapping the hydroquinone intermediate i with pyridine/acetic anhydride (Scheme, pathway B) afforded a 93% yield of the allylic methyl ether 4. This species surprisingly was stable both to silica gel chromatography and brief exposure to acetic acid. However, upon exposure to d,l-camphorsulfonic acid/dichloromethane, 4 readily underwent a 1,4-elimination of methanol to give the desired naphthalene product RS-43179 in essentially quantitive yield.[7]

Finally, a one-pot method for the construction of RS-43179 was realized by employing a different order of experimental procedures (Scheme, pathway C). Specifically, Diels-Alder reaction between 1 and 2 as above gave rise to i, to which was added a catalytic amount of camphorsulfonic acid (in situ production of iii). Acetylation (pyridine/acetic anhydride) afforded the desired RS-43179 in 58% isolated yield.

This methodology is amenable to large scale operation, and offers a highly convergent entry into a variety of beta-halogenated polysubstituted naphthoquinones (and hydroquinones). Further examples of the usefulness of the diene 1 in Diels-Alder chemistry will be reported elsewhere.

EXPERIMENTAL[8]

6-Chloro-2,3-dimethoxy-1,4-naphthalenedione (3):

A benzene (8 mL) solution of 2,3-dimethoxy-2,5-cyclohexadiene-1,4-dione (1.00 g, 5.9 mmol) and 3-chloro-1-methoxy-1,3-butadiene (1.40 g, 12.0 mmol) was stirred for 35 hr under an inert atmosphere at RT. After this time, air was briefly bubbled through the solution (20 min) and the mixture passed through a silica gel plug to afford 1.07 g (72%) of pure 6-chloro-2,3-dimethoxy-1,4-naphthalenedione, mp 127-30°C. PMR ($CDCl_3$): 4.11 ppm (s, 3 H); 4.13 ppm (s, 3 H); 7.66 ppm (dd, 1 H); 8.02-8.05 ppm (m, 2 H). IR (KBr): 1663 cm^{-1}; 1613; 1588.

One-pot Synthesis of RS-43179 (6-Chloro-2,3-dimethoxy-1,4-naphthalenediol, Diacetate)

A dichloromethane (10 mL) solution of 2,3-dimethoxy-2,5-cyclohexadiene-1,4-dione (1.00 g, 5.9 mmol) and 3-chloro-1-methoxy-1,3-butadiene (1.40 g, 12.0 mmol) was stirred for 24 hr at room temperature under an inert atmosphere. After this time, 80 mg of d, l-camphorsulfonic acid was added and the solution stirred an additional 12 hr. The mixture was then concentrated and subsequently dissolved in pyridine (15 mL) and acetic anhydride (3.0 g). After stirring for 5 hr under an inert atmosphere, the solution was concentrated to dryness and taken up into dichloromethane. The organics were washed with water, brine, and then dried (sodium sulfate). Concentration followed by flash chromatography (Hexanes/ethyl acetate 3:1) afforded 1.17 g (58%) of pure 6-chloro-2,3-dimethoxy-1,4-naphthalenediol, diacetate, mp 83-5°C. PMR ($CDCl_3$):2.34 ppm (s, 3 H); 2.36 ppm (s, 3 H); 3.90 ppm (s, 6 H); 7.24 ppm (dd, 1 H); 7.56 ppm (d, 1 H); 7.61 ppm (d, 1H). IR (KBr): 1768 cm^{-1}.

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2. G. H. Jones and J. M. Young, Eur. Patent 0 007 985 A1, Syntex (U.S.A.), Inc., Feb. 20, 1980.

3. G. H. Jones, M. C. Venuti, and J. M. Young, US Patent 4,466,981, Syntex (U.S.A.), Inc., Aug. 21, (1984).

4. Available in one step from commercially available *cis*-1-methoxy-1-buten-3-yne. See: R. N. Kudyakova, S. I. Azimova, E. O. Tsetlina, and A. N. Volkov, Zh. Org. Khim., 10, 949 (1974).

5. M. Matsumoto and H. Kobayashi, J. Org. Chem., 50, 1766 (1985).

6. Diels-Alder reactions with **1** must be conducted under inert atmosphere in order to avoid decomposition of the diene.

7. For similar 1,4-elimination of alcohols from Diels-Alder adducts, see: J. P. Gesson, J. C. Jacquesy, and M. Mondon, Tett Letters, 21, 3351 (1980); J. G. Bauman, R. B. Barber, R. D. Glees, and H. Rapoport, Tett Letters, 21, 4777 (1980).

8. All isolated compounds exhibited elemental analyses within 0.4% of theory.

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