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A Rapid Access to Hydroxylated Benz[*a*]anthraquinones : Hypervalent Iodine Oxidation of β - Naphthols

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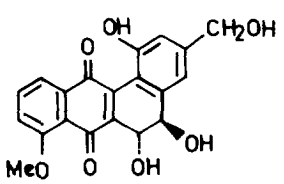
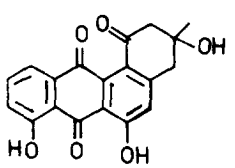
Abstract : Anionic annulation of phthalide sulfones **3** with quinone monoketals **6**, accessible by phenyliodonium diacetate oxidation of naphthols **5**, offers a high yielding regiospecific entry to benz[*a*]anthraquinones **8**. Similar annulation of cyanophthalide **13** with **12**, followed by photooxygenation of **14** results in a complementary route to the basic skeleton **15** of nonaromatic A - ring angucyclines. © 1997, Published by Elsevier Science Ltd. All rights reserved.

Angucyclines, characterized by benz[*a*]anthracenone framework with varying degree of unsaturation and oxygenation (e.g. **1** and **2**) have been emerging as a major subclass of polyketide antibiotics[1]. Today, more than 100 such antibiotics are known in the literature. Whilst the interest in the closely related anthracyclines is waning, the angucyclines have become the focus of intense research activity by virtue of their structural diversity, and interesting biological activity, particularly the vincristine potentiating activity[2] and the antitumor activity[3] against doxorubicin-resistant cell lines.



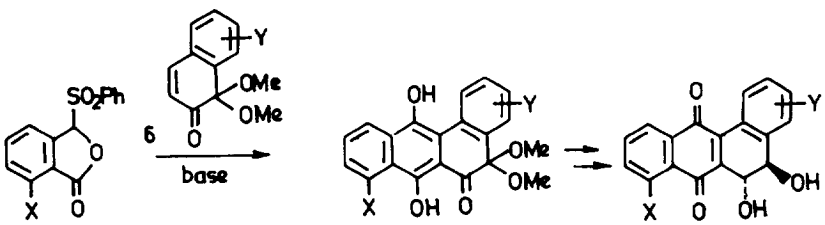
1 (PD116740)



2 (Rabelomycin)

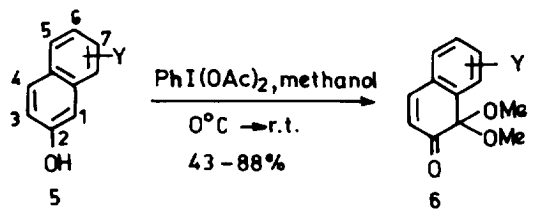
Synthesis in the angucycline family was initiated by Brown and Thomson who had synthesized tetragulol.[4] Soon thereafter, Guingant and Barreto developed an efficient and elegant methodology involving Diels-Alder reaction between a naphthoquinone and a 3-vinylcyclohexenone for the construction of an angular tetracyclic skeleton.[5] This approach has led to total synthesis[6] of several angucyclines, and appears to be the most successful one. A number of other synthetic entries into the benz[*a*]anthraquinone skeleton have recently been reported. These includes: i) directed ortho-metalation-

Friedel Crafts acylation[7], ii) chromium carbene complex benzannulation[8], iii)aldol-type condensation[9] and iv) free radical cyclisation[10]. We were, however, tempted to explore phthalide annulation strategy[11] because of its regiochemical integrity and convergency. Moreover, this strategy has rivalled Diels-Alder approach in the synthesis of linearly fused anthracyclines. It occurred to us if a naphthoquinone monoketal were mounted onto a phthalide sulfone **3**, it would result in the direct formation of benz[*a*]anthraquinone skeleton(Scheme 1) with desired disposition of substituents. Herein, we describe the preparation of quinone monoketals **6** and their utilisation in facile fabrication of a number of hydroxylated benz[*a*]anthraquinones **8**. Extension of this approach to construction of nonaromatic A ring benz[*a*]anthraquinones is also exemplified by the synthesis of **15**.



Scheme 1

Although the chemistry[12] of benzoquinone monoketals is well studied and exploited in the synthesis of many natural products, that of *o*-naphthoquinone-1-ketals is little investigated, possibly due to the dearth of their preparative methods. DDQ or thallium(III) nitrate oxidation of β-naphthols has been of limited preparative use due to poor yields of the products.[13] The recent publication[14] of Malliks has indicated that *o*-naphthoquinone-1-ketals could be conveniently prepared by phenyliodonium diacetate (PIDA) oxidation of β-naphthols. However, this report has dealt with only one example, i.e., the parent member **6a**. In the context of our goal, we have further explored the reaction in details to generalise it. As shown in Table 1, quinone-1-ketals **6** (Scheme 2) can be obtained in good yields from PIDA oxidation of β-naphthols **5** and it is quite general for a number of B-ring substituted β-naphthols. The monoketals **6** are fairly stable, can be purified by rapid silica gel chromatography and stored for weeks. The purities of the products are above 95%, as judged from their PMR spectra. No attempts were made to obtain their analytical samples.



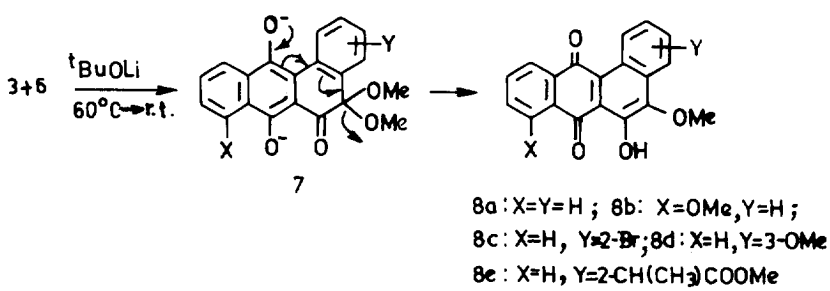
a, Y=H; b, Y=6-Br; c, Y=7-OMe;
d, Y=5-COOMe; e, Y=6-CH(CH3) COOMe

Scheme 2

Table 1. Oxidation of β-naphthols by PIDA

β-Naphthols(5)	Quinone monoketals(6)	yield (%)
5a(Y = H)	**6a**	76
5b(Y = 6-Br)	**6b**	66
5c(Y = 7-OMe)	**6c**	88
5d(Y = 5-COOMe)	**6d**	43
5e(Y = 6-CH(Me)COOMe)	**6e**	52

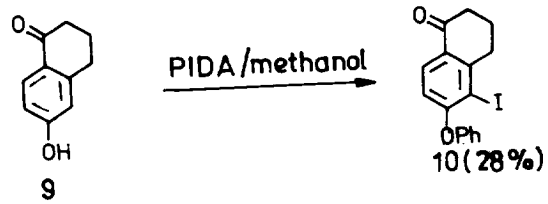
When the phthalide anion, prepared by deprotonation of phthalide sulfone **3a**[15] with ^{t}BuOLi at -60°C, was treated with ketal **6a** (1.0 equiv.), the color of the reaction mixture started turning red indicating the progress of the reaction. After overnight stirring at r.t for 12h, the mixture was worked up to furnish benz[*a*]anthraquinone **8a** (Scheme 3), instead of the corresponding quinol of type **4** (Scheme 1). The product was further transformed to its O - acetyl derivative for its characterisation. It is possible that this unusual product has been formed via expulsion of a methoxide ion from the initially formed annulated quinol dianion **7**. The facile methoxy group elimination from **7** is noteworthy, considering the fact that it would involve a transition state with disrupted A-ring aromaticity. This is the first report of an *o*-naphthoquinone monoketal undergoing successful annulation with a phthalide sulfone synthon, though annulation of *p*-benzoquinones and *o*-benzoquinones has been known in the literature for quite sometime.[11] The possibility of annulation of *o*-naphthoquinone with **3a** has been looked into.[16] However, it never provided a characterisable product.



Scheme 3

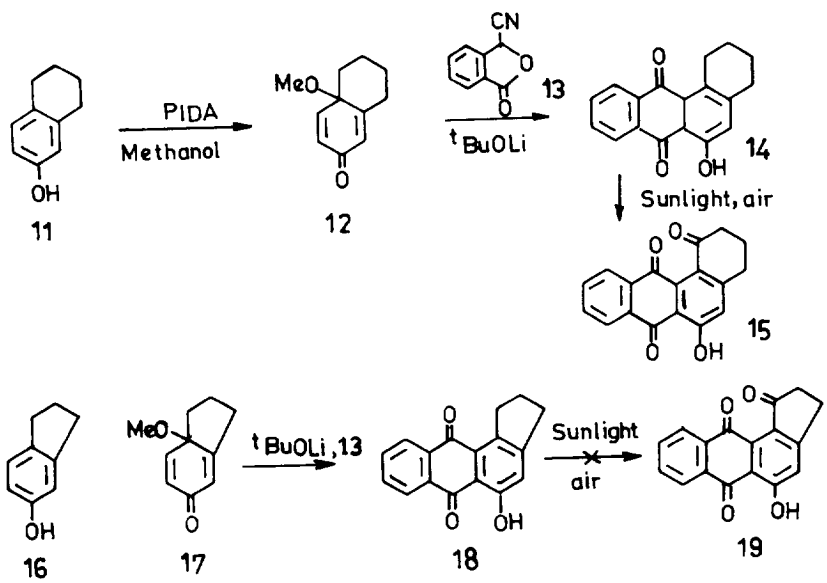
Following the success with **6a**, we examined the other ketals **6b-6e**. Expectedly, the respective annulation-rearrangement products **8b-8e** were obtained in excellent yields, except for **6d**. The failure of the annulation with **6d** may be attributed to the steric effect caused by the carbomethoxy group present in it. The product **8c**, derived from commercially available antiinflammatory drug, naproxen is of special interest since some anthraquinones are used as antirheumatic drugs. The pharmacological activity of this bioconjugate will be reported in due course.

In order to extend the scope of the above approach to nonaromatic A-ring angucyclines, we next examined oxidation of 6 - hydroxy - α - tetralone **9** . Reaction of tetralone **9** with PIDA in methanol



Scheme 4

furnished iodinated phenyl ether **10** (Scheme 4), instead of the desired dimethyl monoketal. The outcome of the reaction is, however, consistent with the results obtained with phenolic compounds with electron withdrawing groups. Hydroxycoumarins and flavones have been shown to give rise to iodinated ethers on the action of PIDA.[17] In an altered approach, we undertook oxidation of hydroxytetralin **11** to permit an entry to nonaromatic A-ring angucyclines. As expected, PIDA oxidation of **11** in methanol provided decalone **12** (67%). Attempts to annulate it with phthalide sulfone **3a** under the conditions described for **8** met with failure. The sulfone was totally destroyed and enone **12** recovered in ~ 35 % yield. Anticipating that the phenylsulfonyl group in **3a** causes steric hindrance with methoxy group and ring methylene group of **12**, we next investigated the reactivity of cyanophthalide **13** towards **12**. The desired annulated product **14** (Scheme 5) was obtained in excellent yield (85 %) using the cyanophthalide. In order to test introduction of the keto function at C_1 of angucyclines, compound **14** was directly exposed to sunlight in chloroform medium according to the pioneering work[18] of Krohn on photooxygenation. The reaction cleanly provided the keto compound **15**[21] in good yield, constituting a new entry to angucycline skeletons. Further extension of this annulation - photooxygenation route was then



Scheme 5

sought for the preparation of cyclopentanone fused analog **19**. Annulation of **13** with enone **17**, prepared by PIDA oxidation of **16** yielded the desired anthraquinone **18** (95%). But the aerial photooxidation of **18** was unsuccessful under a variety of conditions. Studies are in progress to utilise the described methodology for the total synthesis of naturally occurring angucyclines.

In summary, this study illustrates that three key reactions : PIDA oxidation of phenols, phthalide annulation and photooxidation can provide rapid entries to hydroxylated benz[*a*]anthraquinones of angucyclines. Easy accessibility of starting materials, high yields and absolute regiochemical consequence may make these routes competitive with the known approaches to angucyclines.

Experimental

General : Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 883 using KBr pellets for solids and neat for liquids. ^{1}H NMR and ^{13}C NMR spectra were recorded a Brucker-200 using solutions in $CDCl_3$ containing TMS as the internal standard. All J values are given in Hz, chemical shifts in δ and IR frequencies in cm^{-1}. Mass spectra and C,H analytical data were obtained from CDRI, Lucknow. All necessary solvents were purified prior to use. Tetrahydrofuran(THF) was distilled from sodium/benzophenone and pyridine from calcium hydride. Reactions were monitored by thin-layer chromatography using UV detector.

β - Naphthols **5c**[19] and **5d**[20] were prepared by literature methods. β - Naphthols **5b**, and phenols **11** and **16** are commercial samples. Compound **5c** was prepared from a commercial sample of naproxen by *O*-demethylation and esterification sequence.

***PIDA oxidation of β - naphthols* 5**

To a solution of a β -naphthol (3 mmol) in dry methanol (50 mL) at 0°C under N_2 atmosphere was added phenyliodonium diacetate (2.2 equiv.) in two portions at 2 hr interval and the resulting solution was allowed to stir at r.t. for 24 h. The reaction was then quenched with sat. sodium bicarbonate solution (20 mL). Bulk of the solvent was removed under reduced pressure and the residue was subjected to usual work-up (washing with brine, drying over Na_2SO_4 and concentrating under vacuo). The products were purified by chromatography on silica gel. For the oxidation of phenols **11** and **16,** 1.2 equiv. of PIDA was used in one portion.

Compound **6b**: oil; IR, 1687; ^{1}H NMR 7.55 (br s, 2 H, Ar-H), 7.43(s, 1 H), 7.20(d, 1 H, J = 10, 4-H), 6.13(d, 1 H, J = 10, 3-H), 3.25(s, 6 H, 2xOCH_3). ^{13}C NMR , 194.7(C=0), 142.3(CH), 136.5(C), 133.2(C), 132.6(CH), 132(CH), 129.8(CH), 126.3(CH), 123.8(C), 95.1(C), 51.8(CH_3).

Compound **6c**: oil; IR 1682; ^{1}H NMR 7.30-7.2(m, 3 H, Ar-H and enone H), 6.88(dd, 1 H, J = 2.5, 8.4), 6.99(d, 1 H, J = 10, 3-H), 3.87(s, 3 H, Ar-OMe), 3.27(s. 6 H, 2x OMe).

Compound **6d**: oil IR 1719, 1686; ^{1}H NMR 8.38(d, 1 H, J = 10, 4-H), 7.93(dd, 1 H, J = 7.8, 1.4, 6-H), 7.88(d, 1 H, J = 7.8, 8-H), 7.49(t, 1 H, J = 7.8, 7-H), 6.20(d, 1 H, J=10, 3-H), 3.93(s, 3 H, $COOCH_3$), 3.25(s, 6 H, 2 x OCH_3).

Compound **6e**: oil; IR 1729, 1679; ^{1}H NMR 7.65(d, 1 H, J = 8, 4-H), 7.35(dd, 1 H, J = 2,8, 6-H), 7.26(d, 1 H, J = 8, 8-H), 7.23(brs, 1 H, 7-H), 6.09(d, 1 H, J = 8, 3-H), 3.73(q, 1 H, J = 7, CHCOOMe), 3.68(s, 3 H, $COOCH_3$), 3.27(s, 6 H, 2xOCH_3), 1.52(d, 3 H, J = 7, C-CH_3).

Compound **10**: mp. 98-99°C; IR 1675; ^{1}H NMR 7.97(d, 1H, J = 8.5, 8-H), 7.45-7.3(m, 2 H, Ph-H), 7.25-7.15(m, 1 H, Ar-H), 7.0-6.95(m, 2 H, Ar-H), 6.69(d, 1 H, J = 8.5, 7-H), 3.05(t, 2 H, J = 6, 2-H), 2.63(dd, 2 H, J = 7.5, 6, 4H), 2.25-2.1(m, 2 H, 3-H); ^{13}C NMR, 196.6(C=O), 161.1(C), 155.4(C), 149.5(C), 130.1(CH), 129.3(C), 129.1(CH), 124.7(CH), 119.8(CH), 115.3(CH), 94.4(C), 37.8(CH_2), 36.3(CH_2), 22.8(CH_2).

Compound **12**: Yield, 67%; oil; IR 1669; ^{1}H NMR 6.67(d, 1H, J = 10, 4-H), 6.30(dd, 1 H, J = 2,10, 3-H), 6.19(m, 1 H, 1-H), 3.04(s, 3 H, OCH_3), 2.43-2.2(m, 2 H, ring CH_2), 2.2-1.8(m, 3 H, ring CH_2's), 1.65-1.55(m, 1 H, ring CH_2), 1.45-1.2(m, 2 H, ring CH_2); ^{13}C NMR 185.7(C=0), 162.6(C), 150.8(CH), 130.8(CH), 126.4(CH), 73.6(C), 51.6(CH_3), 39.2(CH_2), 27.9(CH_2), 20.2(CH_2).

Compound **17**: Yield, 41%; oil; IR 1672; ^{1}H NMR 6.73(d, 1H, J = 10, 4-H), 6.28(dd, 1 H, J = 2,10,5H), 6.15(brs, 1 H, 7-H), 3.05(s, 3 H, OCH_3), 2.75-2.55(m, 1 H, cyclopent-H), 2.55-2.35(m, 1 H, cyclopent-H), 2.35-1.8(m, 3 H, cyclopent-H), 1.65-1.5(m, 1 H, cyclopent-H).

***General Annulation Procedure for* 8**

A stirred solution of tert-butanol(9.0 mmol) in dry THF (20 mL) under an Ar atmosphere was cooled to 0°C and treated with n-butylithium (9.0 mmol) in hexane. After the mixture was stirred for about 10 min following the addition, the solution was cooled to -60°C($CHCl_3$/liq.N_2 bath) and an appropriate sulfone **3** (3 mmol) in THF (10 mL) was added dropwise over 5 min. After an additional 15 min., an appropriate quinone monoketal **6** (3 mmol) in THF (5 mL) was introduced. The resulting deep purple mixture was stirred at -60°C for 3 h and then at ambient temperature for 12 h. It was then quenched with 10% HCl (5 mL) and concentrated at reduced pressure to nearly half of its volume. At this point, a deep colored solid **8** separated. This was filtered and washed with water several times. The filtrate was extracted with ethyl acetate (3 x 50 mL). The combined extract was washed (20 mL) brine, dried (Na_2SO_4) and then evaporated to give a gummy solid which on silica gel chromatographic purification furnished the second lot of **8**. Compound **14** and **18** were prepared according to this procedure but using cyanophthalide **13**[12] in the place of **3**.

Compound **8a**: Yield, 82%; mp 154°C; IR 1642; ^{1}H NMR 12.77(s, 1 H), 9.55-9.50(m, 1 H, 1-H), 8.35-8.15(m, 3 H, Ar-H), 7.85-7.7(m, 2 H, Ar-H), 7.60-7.5(m, 2 H, Ar-H), 4.21(s, 3 H, OCH_3); ^{13}C NMR 190.8(C), 184.4(C), 148.5(C), 148.4(C), 135.1(C), 135(CH), 133.3(CH), 132.9(C), 132.0(C), 129.0(CH), 128.5(CH), 128.4(CH), 127.3(CH), 127(C), 126.3(CH), 124.5(C), 121.4(CH), 120.3(C), 61.2(CH_3), m/z, 304(M^+), 100%). Anal. C, 75.2%; H 4.1%; Calcd for $C_{19}H_{12}O_4$; C,75%, H,4%.

Compound **8b**: Yield 98%; mp 210°C; IR 1634; ^{1}H NMR 12.87(s, 1 H, OH), 9.4-9.35(m, 1 H, 1-H), 8.2-8.1(m, 1 H, 11-H), 9.86(dd, 1 H, J = 2,8, Ar-H), 7.7(t, 1 H, J = 8, Ar-H), 7.6-7.45(m, 2 H, ArH), 7.24(d, 1 H, J = 8, Ar-H), 4.17(s, 3 H, 5-OCH_3), 4.04(s, 3 H, 8-OCH_3); ^{13}C NMR , 190.3(C), 184.6(C), 160.2(C), 148.5(C), 137.4(C), 136.1(CH), 132.4(C), 128.8(CH), 128.3(CH), 128.1(CH), 126.3(C), 124(C), 121.5(C), 121.3(CH), 119.9(CH), 117(CH), 61.2 (CH_3), 56.6 (CH_3). Two carbons are missing m/z, 334 (M^+, 100 %); Anal. C, 72.2%; H 4.3%; Calcd. for $C_{20}H_{14}O_5$ C, 71.9 %; H,4.2%.

Compound **8c**: Yield, 95%; mp 240°C; IR 1638; ^{1}H NMR 12.85(s, 1 H, OH), 9.87(d, 1 H, J = 2, 1-H), 8.32-8.27(m, 2 H, Ar-H), 8.09(d, 1 H, J = 9, Ar-H), 7.9-7.7(m, 2 H, Ar-H), 7.65(dd, 1 H, J = 2, 9, Ar-H); m/z, 384(M^+, 100%).

Compound **8d**: Yield, 52%; mp 187-188°C; IR 1625; ^{1}H NMR 12.88(s, 1 H, OH), 9.43(d, 1 H, J = 9.6, 1-H), 8.3-8.2(m, 2 H, Ar-H), 7.85-7.7(m, 2 H, ArH), 7.39(d, 1 H, J = 2.5, Ar-H), 7.20(dd, 1 H, J = 2.5, 9.6, Ar-H), 4.19(s, 3 H, OCH_3), 3.98(s, 3 H, OCH_3. ^{13}C NMR 190.4(C), 184.5(C), 160.3(C), 149.2(C), 146.6(C), 135.2(C), 134.7(CH), 133.2(CH), 132.2(C), 130.6(CH), 127.3(CH), 126.3(CH), 124.7(C), 122.9(C), 122(CH), 118.2(C), 98.6(CH), 60.8(CH_3), 55.3(CH_3). m/z 334(M^+, 100%). Anal C, 71.9%, H, 4.3%; Calcd for $C_{20}H_{14}O_5$C, 71.9%, H, 4.2%

Compound **8e**: Yield 55%; mp 137-138°C; IR 1732, 1638;^{1}H NMR 12.81(s, 1 H), OH), 9.54(d, 1 H, J = 2, 1-H), 8.35-8.25(m, 2 H, 8, 11-H), 8.18(d, 1 H, J = 8, 4H), 7.86-7.75(m, 2 H, 9,10-H), 7.56(dd, 1 H, J = 1.5, 8, 3-H), 4.2(s, 3 H, OCH_3), 3.98(q, 1 H, J = 7, 2'-CH_3); ^{13}C NMR , 190.8(C), 181.3(C), 174.6(C), 148.6(C), 148.5(C), 140.7(C), 135.4(C), 135.1(C), 135(CH), 133.2)CH), 132(CH), 130.5(C), 130(C), 128.7(CH), 127.2(CH), 127(CH), 126.3(CH), 122(CH), 121.2(C), 61.2(CH_3), 52.1(CH_3), 45.9(CH), 18.3(CH_3); m/z 390(M^+);

Compound **14**: Yield 85%; mp 144-145°C; IR 1634, 1539; ^{1}H NMR 13.05(s, 1 H, OH), 8.27-8.15(m, 2 H, 8,11-H), 7.82-7.68(m, 2 H, 9,10-H), 7.01(s, 1 H, 5-H), 3.26(brs, 2 H, 1-H), 2.88(brs, 2 H, 4-H), 1.82(m, 4 H, 2,3 H); ^{13}C NMR 188.7(C), 184.7(C), 160.9(C), 149.8(C), 135.1(C), 134.3(CH), 133.2(CH), 132.5(C), 130.4(C), 127.3(CH), 126.2(CH), 124.4(CH), 115.5(C), 31.7(CH_2), 29.0(CH_2), 23.4(CH_2), 21.9(CH_2). m/z, 278(M^+, 100%).

Compound **18**: Yield, 95%; mp 161-162°C; IR 1629; ^{1}H NMR 13.11(s, 1 H, OH), 8.35-8.22(m, 2 H, 7-10H), 7.82-7.75(m, 2 H, 8,9-H), 7.17(s, 1 H, 4-H), 3.42(t, 2 H, J = 8, 1-H), 2.97(t, 2 H, J = 8, 3-H), 2.25-2.10(m, 2 H, 2-H); ^{13}C NMR 188.1(C), 183.8(C), 162.9(C), 157.3(C), 140.2(C), 134.2(CH), 134(C), 133.6(CH), 133.2(C), 127.7(C), 127(CH), 126.5(CH), 119.7(CH), 114.4(C), 33.8(CH_2), 32.9(CH_2), 24.9(CH_2); m/e 264(M^+, 100%). Anal. C, 76.9%; H 4.7%, Calcd for $C_{17}H_{12}O_3$; C, 77.2%, H, 4.6%.

***Photooxygenation of compound* 14** : A solution of **14** (~ 100 mg) in chloroform (10 mL) taken in a test tube was exposed directly to sunlight. When the reaction deemed complete by tlc (~ 5-6 h), the solution was concentrated and chromatographed to furnish compound **15** as orange crystals in 88% yield. The spectral data were in good agreement with the reported values[20].

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