Pergamon

Tetrahedron Letters 39 (1998) 2253–2256

TETRAHEDRON
LETTERS

CONTROL OF RELATIVE STEREOCHEMISTRY OF QUATERNARY CARBON CENTERS VIA THE INTRAMOLECULAR DIOXENONE PHOTOCYCLOADDITION: AN APPROACH TO THE SYNTHESIS OF SAUDIN◆

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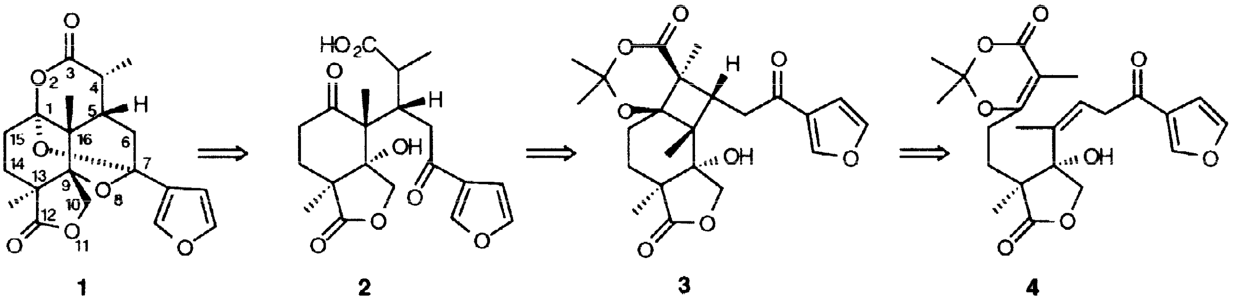
Received 30 July 1997; accepted 23 January 1998

Abstract: The results of a model study are reported establishing that the intramolecular dioxenone photocycloaddition reaction leads to a uniquely efficient approach for the establishment of the correct relative stereochemical relationship between the two quaternary carbons in saudin.

Saudin, **1**, isolated in 1985 by Mossa, et al.,[1] from the leaves of the toxic plant *Cluytia richardiana*, is noteworthy both for its unusual structure as a highly oxygenated secolabdane with a unique bis-ketal backbone, and for its reported hypoglycemic activity. We report herein the results of a model study establishing that the intramolecular dioxenone photocycloaddition reaction[2] leads to a uniquely efficient approach for the establishment of the correct relative stereochemical relationship between the two quaternary carbons (C-13 and C-16) in saudin.

Scheme 1

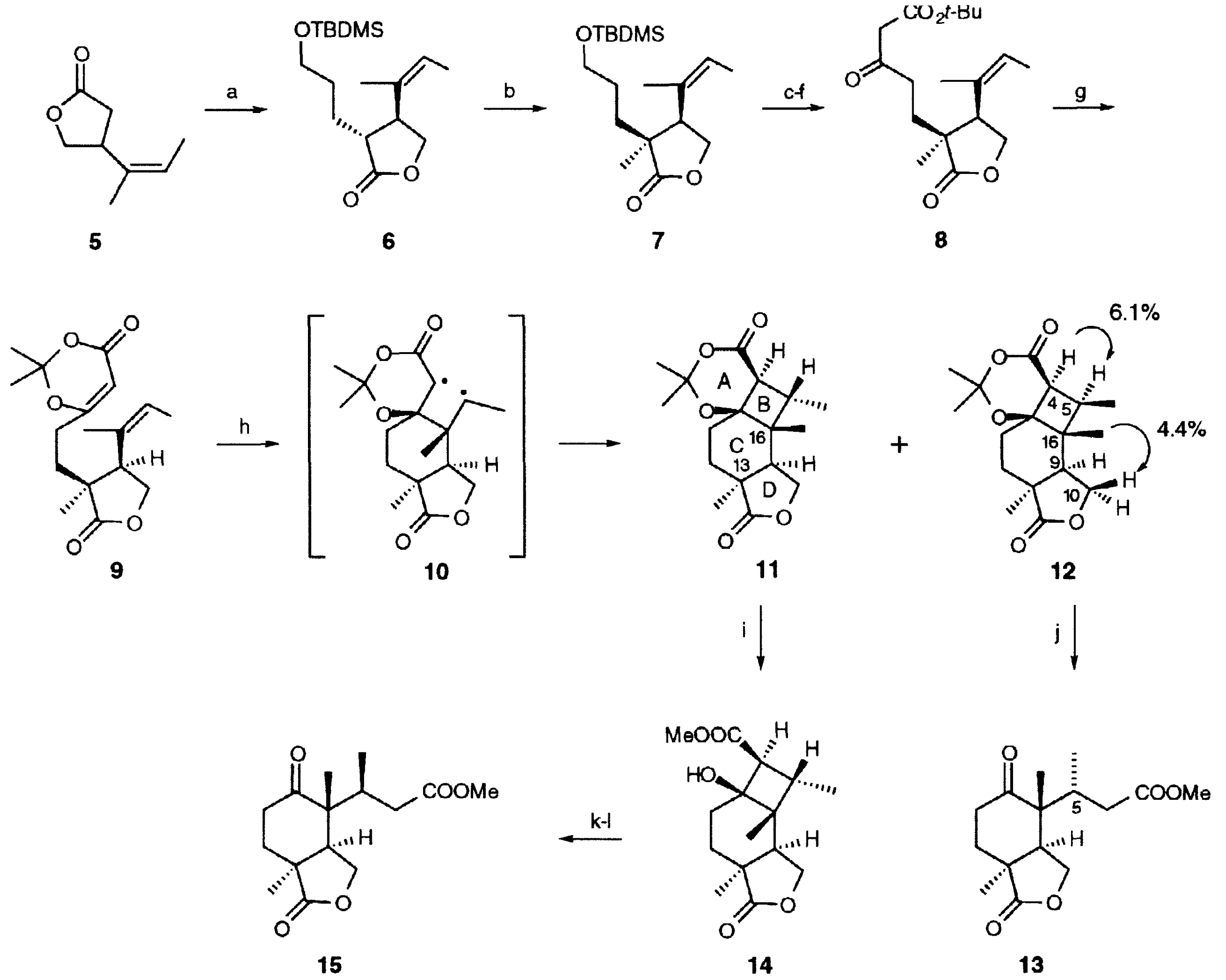


The retrosynthetic analysis that we have employed for the construction of saudin is outlined in Scheme 1. Disconnection of the bisketal of **1** leads to the diketone **2**, which could result from the photocycloaddition of the dioxenone photosubstrate **4** and fragmentation of the resulting cyclobutane photoadduct, **3**. To establish the viability of the dioxenone photocycloaddition methodology for the synthesis of this highly congested carbon network, the photoaddition of the model substrate, **9**, was examined, the preparation of which is outlined in Scheme 2.

◆ Dedicated to our friend and colleague Professor Eli Loewenthal.

PII: S0040-4039(98)00285-8

Scheme 2



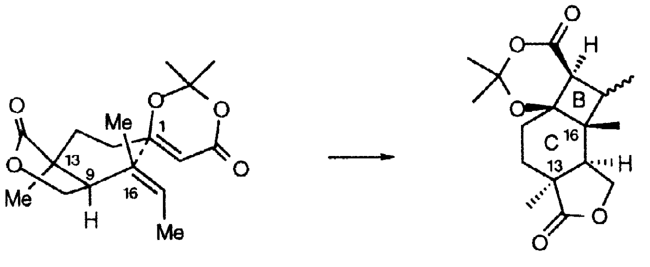
a) LDA, $I(CH_2)_3OTBDMS$ (65%); b) LDA, MeI (100%); c) TBAF (73%); d) Jones (67%); e) CH_2N_2 (100%); f) $LiCH_2COOt$-Bu (69%); g) TFAA, TFA, Me_2CO (79%); h) hν, Pyrex, $Me_2CO/MeCN$, 0 °C (97%); i) MeOH, TsOH, reflux, 54%; j) MeOH, TsOH, reflux, 61%; k) KOH/MeOH; l) CH_2N_2 (85% over 2 steps)

Reaction of the conjugate base of lactone **5** (available in 92% yield by addition of lithium di-2-*trans*-butenylcuprate[3] to butenolide[4]) with 1-*t*-butyldimethylsilyloxy-3-iodopropane[5] gave trans-disubstituted lactone **6**. Reaction of the enolate derived from **6** with iodomethane led to the stereoselective formation of **7**, in which the methyl group adds trans to the alkenyl group on the enolate derived from **6**, a result which is both consistent with previous results[6] and that has been unambiguously established by the X-ray structure of the derived photoadduct, **11**. Desilylation of **7** followed by Jones oxidation and treatment of the resulting acid with diazomethane gave the methyl ester which was exposed to an excess of the lithium enolate of *t*-butyl acetate[7] to afford β-keto ester **8**. Exposure of the keto ester to dioxenone-forming conditions (TFAA/TFA/Me_2CO) provided the photosubstrate, **9**.[8]

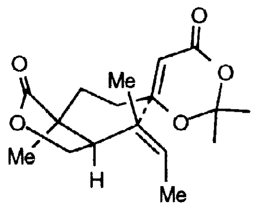
Irradiation of **9** [3 mM in $MeCN/Me_2CO$ (9:1), 450 W medium pressure Hanovia Hg lamp, Pyrex filter, 0 °C, 2 h] led to the formation of a 2.5:1 mixture of diastereomeric products, **11** and **12** in 97% total isolated yield.[9] The structure and stereochemistry of the major product, **11**, was confirmed by X-ray crystallographic analysis,[10] which established that the formation of **11** had proceeded with the establishment of the desired trans relationship of the quaternary methyl groups at C-13 and C-16 (saudin numbering).

The relative configuration of the minor isomer, **12**, was established by a series of nOe experiments. Strong reciprocal nOe enhancements were observed as shown in Scheme 2. A strong nOe was observed between the C-16 methyl and the C-10β hydrogen, which confirms the same C-13/C-16 relative stereochemistry as that found in **11**.[11] There was also a reciprocal nOe between the C-4 and C-5 methines as well as an absence of nOe between the C-5 methine hydrogen and the C-16 methyl group. That the minor product, **12**, is epimeric with **11** at C-5 indicates that the stereochemistry of the trisubstituted alkene in **9** is lost during the course of the photocycloaddition as a consequence of the intermediacy of biradical intermediate **10**[12] in the triplet-sensitized dioxenone photoreaction.[13]

Two additional features of the stereochemical consequences of the intramolecular cycloaddition of **9** deserve comment. The establishment of the relative stereochemistry of the C-13/C-16 quaternary centers in **11** and **12** can be attributed to the orientation of photosubstrate **9** shown in A (vide infra). As a consequence of $A^{1,3}$-allylic strain,[14] the orientation of the trisubstituted olefin in A should be fixed as indicated. Approach of the dioxenone to the alkene in such an orientation would necessarily establish the desired trans relative stereochemistry of the C-13 and C-16 methyl groups as was observed in the formation of both **11** and **12**. In addition, both photoadducts **11** and **12** contain a cis-fused bicyclo[4.2.0]octane (B/C ring fusion). This stereochemical outcome can be attributed to the ca. 1.6 kcal/mol difference between the two lowest energy orientations, A and B, of photosubstrate **9**, both of which have boat-like orientations of the nascent six-membered ring (calculated using Chem 3D Pro MM2 with a 2.5 Å restriction on the C-1/C-16 interatomic distance[15]). The trans(B/C)-fused photoproduct that would result from cycloaddition *via* B is not observed.



A **11/12**



B

The epimeric photoadducts **11** and **12** were subjected to fragmentation conditions to generate the bicyclic ring system corresponding to **2** (Scheme 2). Heating **12** to reflux in methanol in the presence of catalytic *p*-toluenesulfonic acid afforded ester **13** in 61% yield. Subjecting photoadduct **11** to the same reaction conditions afforded instead the cyclobutanol product, **14**, the structure of which was confirmed by X-ray crystallography. Exposure of **14** to basic conditions (KOH/MeOH) followed by esterification of the intermediate carboxylic acid with ethereal diazomethane led to the formation of keto ester **15**, which is epimeric with **13** at C-5 (Scheme 2).

This highly stereoselective construction underscores the utility of the intramolecular dioxenone photoaddition-fragmentation reaction for the synthesis of highly substituted, stereochemically dense carbocyclic ring systems. Efforts in our laboratory directed toward the completion of the synthesis of saudin using this approach are currently underway and our results will be reported in due course.

Acknowledgment. Support from the National Institutes of Health, SmithKline Beecham, Pfizer and Wyeth-Ayerst is gratefully acknowledged. We would like to thank Dr. Pat Carroll for the determination of the X-ray crystal structures of **11** and **14**.

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[9] All new compounds were characterized by full spectroscopic (NMR, IR, high resolution MS) data. Yields refer to spectroscopically and chromatographically homogeneous (>95%) materials. Spectral data for photosubstrate **9:** mp 79-80 °C; R_f 0.33 (50% EtOAc/hexane); ^{1}H NMR (500 MHz): δ 5.46 (q, *J* = 6.5 Hz, 1 H), 5.18 (s, 1 H), 4.40 (dd, *J* = 6.7, 9.5 Hz, 1 H), 4.18 (dd, *J* = 3.3, 9.5 Hz, 1 H), 3.28 (dd, *J* = 3.3, 6.4 Hz, 1 H), 2.46 (m, 1 H), 2.14 (m, 1 H), 1.86 (dt, *J* = 4.9, 13.5 Hz, 1 H), 1.65 (m, 12 H), 1.50 (dt, *J* = 4.3, 13.5 Hz, 1 H), 1.31 (s, 3 H); ^{13}C NMR (125 MHz) δ 180.47, 171.24, 161.08, 131.30, 125.28, 106.40, 93.12, 68.32, 46.02, 44.29, 28.72, 28.21, 24.99, 24.88, 21.58, 20.80, 13.82; FTIR (thin film, cm^{-1}): 2972, 2939, 1768, 1728, 1636, 1459, 1389, 1273, 1204, 1162, 1087, 1015. Exact mass calculated for $C_{17}H_{24}O_5$+NH_4 (CI): 309.1967, found 309.1976; photoadduct **11**: mp 208-210 °C; R_f 0.17 (50% EtOAc/hexane); ^{1}H NMR (500 MHz): δ 4.41 (dd, J = 6.5, 10.0 Hz, 1 H, H-10α), 4.10 (d, J = 10.1 Hz, 1 H, H-10β), 2.39 (d, J = 9.3 Hz, 1 H, H-4), 2.31 (dq, J = 7.2, 9.1 Hz, 1 H, H-5), 2.04-2.09 (m, 2 H), 1.71 (m, 1 H), 1.54 (s, 3 H), 1.51 (s, 3 H), 1.38-1.48 (m, 2 H), 1.27 (s, 3 H, Me-13), 0.98 (m, 6 H, Me-16, Me-5); ^{13}C NMR (125 MHz): δ 182.21, 169.79, 106.15, 76.59, 67.36, 44.55, 44.01, 42.89, 40.13, 31.10, 29.17, 28.74, 24.93, 23.50, 16.11, 13.05; FTIR (thin film, cm^{-1}): 2973, 2937, 2874, 1756, 1725, 1456, 1389, 1379, 1304, 1280, 1207, 1148, 1121, 1101, 1064 . Exact mass calculated for $C_{17}H_{24}O_5$ +NH_4 (CI) 326.1967, found 326.1971; photoadduct **12**: mp 111-115 °C; R_f 0.28 (50% EtOAc/hexane); ^{1}H NMR (500 MHz): δ 4.28 (dd, *J* = 9.5, 9.5 Hz, 1 H, H-10α), 3.85 (dd, *J* = 9.7, 9.7 Hz, 1 H, H-10β), 2.93 (d, *J* = 10.7 Hz, 1 H, H-4), 2.58 (dq, *J* = 7.2, 10.6 Hz, 1 H, H-5), 2.22 (dd, *J* = 9.7, 9.7 Hz, 1 H, H-9), 2.12 (m, 1 H), 2.03 (m, 1 H), 1.71-1.81 (m, 2 H), 1.53 (s, 3 H), 1.50 (s, 3 H), 1.37 (s, 3 H, Me-13), 1.05 (d, *J* = 7.2 Hz, 3 H, Me-5), 0.89 (s, 3 H, Me-13); ^{13}C NMR (125 MHz): δ 183.05, 168.58, 105.03, 74.69, 68.40, 46.81, 45.42, 41.51, 40.93, 34.42, 32.57, 28.93, 28.40, 27.00, 15.48, 10.32; FTIR (thin film, cm^{-1}): 2989, 2940, 1768, 1739, 1467, 1387, 1313, 1280, 1264, 1218, 1188, 1126, 1093, 1048. Exact mass calculated for $C_{17}H_{24}O_5$ +NH_4 (CI) 326.1967, found 326.1975.

[10] Compound **11**, $C_{17}H_{24}O_5$, crystallizes in the orthorhombic space group Pbca (systematic absences hk0: h=odd, 0kl: k=odd, and h0l: l=odd) with a=12.6990(4)Å, b=24.545(1)Å, c=10.4280(4)Å, V=3250.4(2)Å^3, Z=8 and d_{calc}=1.260 g/cm^3. X-ray intensity data were collected on an Rigaku R-AXIS IIc area detector employing graphite-monochromated Mo-K_α radiation (λ=0.71069 Å) at a temperature of 295°K.

[11] These relationships were elucidated by identification of the C-13 methyl group and the hydrogens at C-9, C-10α, and C10β by a series of reciprocal nOe experiments.

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