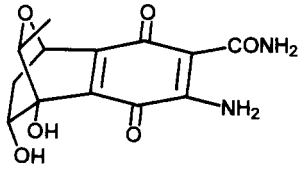
Communications

Total Synthesis of (±)-Sarubicin A (U-58,431)

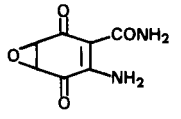
Summary: The first total synthesis of (±)-sarubicin A (U-58,431) has been achieved.

Sir: The antibiotic U-58,431[1a] (sarubicin A)[1b] has been isolated from the culture filtrates of *Streptomyces* strains in 1980 and reported to be active against Gram-positive and -negative bacteria in vitro. The structure 1 determined



1

by X-ray crystallography is unique in that the 1,4-benzoquinone ring possesses the same array of amino and carboxamide groups found with the antibiotic G-7063-2 (**2**)[2] as well as the same 2-oxabicyclo[2.2.2]oct-5-ene skeleton present in granaticin (**3**).[3] We report here the first total



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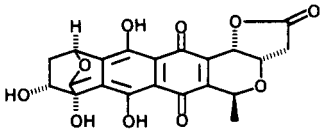

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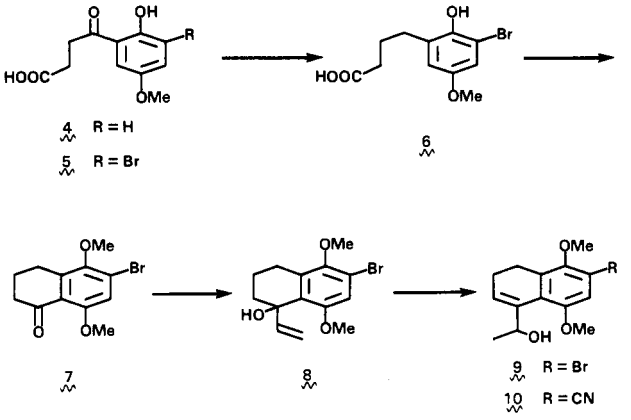
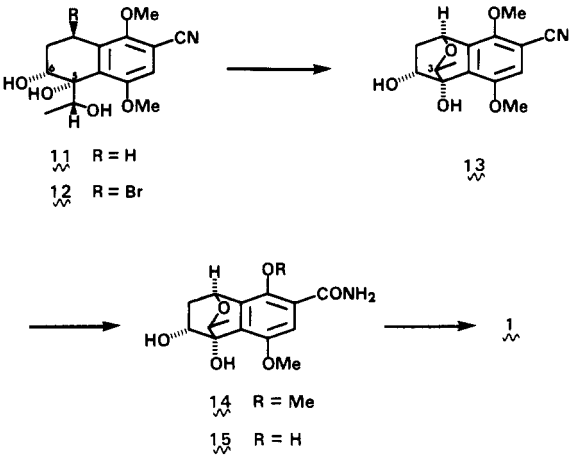
synthesis of the racemate of this synthetically attractive target molecule utilizing the methodology previously developed in these laboratories for the construction of the oxabicyclic system.[4]

3-(2,5-Dimethoxybenzoyl)propionic acid[5] was subjected to selective demethylation ($AlCl_3$/MeCN/65 °C; 70%), and the resulting phenol **4**,[6] mp 145 °C, was brominated (Br_2/HOAc/NaOAc/room temperature; 81%) to give the bromophenol **5**, mp 191 °C (Scheme I). Conversion of the keto group in **5** into the methylene group was cleanly achieved[7] by the method of Minami.[8] Thus, the compound **5** was first acetylated (5 equiv Ac_2O/5 equiv 5%

Scheme I



Scheme II



NaOH/ice/3 min) and then the crude acetate was treated with 4 equiv of $NaBH_4$ (aqueous THF/15 °C/1 h) to furnish **6**, mp 151 °C, in 92% yield. O-Methylation of **6** (Me_2SO_4/aqueous KOH/room temperature; 83%) followed by intramolecular acylation (95% H_2SO_4/70–80 °C/30 min; 64%) provided the tetralone **7**, bp 160–170 °C (0.2 torr), which in turn was reacted with vinylmagnesium bromide to give the vinyl carbinol **8** (97%). The compound **8** was then transformed to the isomeric allyl alcohol **9** by the following sequence of reactions in 54% overall yield: (i) oxymercuration–demercuration[9] ($Hg(OAc)_2$/aqueous THF; $NaBH_4$/3 N NaOH); (ii) selective acetylation of the secondary hydroxyl group of the resulting α-glycol (Ac_2O/pyridine/room temperature); (iii) dehydration ($SOCl_2$/pyridine/O °C/20 min); (iv) hydrolysis of the acetate group (NaOH/MeOH).[10] Replacement of the

(1) (a) Slechta, L.; Chidester, C. G.; Reusser, F. *J. Antibiot.* **1980**, *33*, 919–923. (b) Reinhardt, G.; Bradler, G.; Eckardt, K.; Tresselt, D.; Ihn, W. *Ibid.* **1980**, *33*, 787–790. Tresselt, D.; Eckardt, K.; Ihn, W.; Radics, L.; Reinhardt, G. *Tetrahedron* **1981**, *37*, 1961–1965. Identity of U-58,431 with sarubicin A has been confirmed by the Upjohn group by direct comparison of both samples (private communication from Dr. Slechta).

(2) Noble, M.; Noble, D.; Sykes, R. B. *J. Antibiot.* **1977**, *30*, 455–459.

(3) Keller-Schierlein, W.; Brufani, M.; Barcza, S. *Helv. Chim. Acta* **1968**, *51*, 1257–1268. Brufani, M.; Dobler, M. *Ibid.* **1968**, *51*, 1269–1275.

(4) Sudani, M.; Takeuchi, Y.; Yoshii, E.; Kometani, T. *Tetrahedron Lett.* **1981**, *22*, 4253–4256.

(5) Moore, J. A.; Rahm, M. *J. Org. Chem.* **1961**, *26*, 1109–1111. Momose, T.; Oya, H.; Ohkura, Y.; Iwasaki, M. *Pharm. Bull.* **1954**, *2*, 119–122.

(6) Satisfactory spectral (^1H NMR, mass, IR) data were obtained on all new compounds. Key compounds were also characterized by elemental analyses.

(7) The reduction was initially attempted on the *O*-methyl ether of **5** by standard methods (Et_3SiH/F_3CCOOH: West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* **1973**, *38*, 2675–2681) and Huang-Minlon reduction, but the yields were less than 10%.

(8) Minami, N.; Kijima, S. *Chem. Pharm. Bull.* **1979**, *27*, 816–820, 1490–1494.

(9) Brown, H. C.; Geoghegan, P., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522–1524.

(10) Transformation of **8** to **9** was also carried out by the following procedures in 20% overall yield: (i) Sharpless epoxidation (*t*-BuOOH/$VO(acac)_2$/benzene/reflux),[11] (ii) $LiBHEt_3$ reduction,[12] (iii) the acetylation–dehydration–hydrolysis sequence.

(11) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63–74. Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136–6137.

(12) Krishnamurthy, S.; Schubert, R. M.; Brown, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 8486–8487.

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bromine atom in **9** by cyano group was accomplished by the reaction with CuCN (*N*-methylpyrrolidone/150 °C/3 h; 47%)[13] to give the nitrile **10**. Catalytic osmylation (OsO_4/$Me_3N(O)$/*t*-BuOH/70 °C/1.5 h; 96%)[14] of **10** provided 5*R**,6*R**,1′*R** triol **11**,[15] mp 155 °C, as a single stereoisomer.[16]

Oxidative cyclization of the key intermediate **11** to the 2-oxabicyclo[2.2.2] compound **13**,[15] mp 163.5 °C, was achieved in 92% yield by the following improved procedure:[4] (i) trimethylsilation (excess MeCH=C(OMe)-$OSiMe_3$/CH_2Cl_2/reflux/20 min),[17] (ii) benzylic bromination (NBS/CCl_4/AIBN/sunlamp/60 °C/1 h; then HCl–THF to give **12**;[15] 96%), (iii) dehydrobromination ($AgClO_4$/THF/room temperature/20 min; 96%). The orientation of C(3)-Me in **13** as depicted (Scheme II) was supported by the ^1H NMR spectrum, which showed C(3)-Me at δ 0.86 and C(3)-H at δ 3.77.[18] The nitrile **13** was then converted to the carboxamide **14**, mp 207 °C, in 90% yield by treatment with alkaline hydrogen peroxide.

The final stage of the synthesis, oxidation of **14** to the corresponding *p*-benzoquinone and subsequent introduction of amino group, turned out not to be straightforward. When **14** was converted to the cyclic 4,8-carbonate and treated with either ceric ammonium nitrate (CAN)[19] or AgO,[20] the substrate was recovered unchanged, in contrast to the case of a model compound, 1,4-dimethoxy-5,6,7,8-tetrahydronaphthalene-2-carboxamide, which did undergo facile oxidation to the corresponding benzoquinone. Consequently, **14** was subjected to demethylation (MeS-Li/DMF/155 °C/2 h; 70%),[21] and the resulting phenol **15** was reacted with CAN. Although **15** was readily oxidized to quinone, undefined overreactions associated with the free position ortho to the carboxamide group was difficult to suppress. However, after extensive investigations on the reaction course, we eventually succeeded in obtaining the target compound by carring out the controlled oxidation–in situ amination. Thus, **15** was first reacted with CAN (2 equiv) in MeCN at room temperature, and immediately after the disappearance of **15** (monitored by ^1H NMR or TLC), the reaction mixture was treated with NH_3/MeCN to give (±)-**1**, which was isolated by silica gel chromatography in 74% yield. The structure of the synthetic **1**, mp 214–215 °C, was confirmed by comparison of the spectral data (^1H NMR and mass) and the chromatographic behaviors (TLC and HPLC) with those of the natural product.

Acknowledgment. We thank Dr. L. Slechta (The Upjohn Company) for generous supply of the antibiotic U-58,431 and Dr. D. Tresselt (Akademie der Wissenschaften der DDR) for providing ^1H and ^{13}C NMR spectral data of sarubicin A.

Registry No. **1**, 87392-60-7; **4**, 75501-54-1; **5**, 87338-25-8; **6**, 87338-26-9; **7**, 87338-27-0; **8**, 87338-28-1; **9**, 87338-29-2; **10**, 87338-30-5; **11**, 87338-31-6; **12**, 87338-32-7; **13**, 87338-33-8; **14**, 87338-34-9; **15**, 87338-35-0; 3-(2,5-dimethoxybenzoyl)propionic acid, 1084-74-8; vinyl bromide, 593-60-2.

Supplementary Material Available: Spectral and Analytical data for compounds **4**–**15** and **1** (4 pages). Ordering information is given on any current masthead page.

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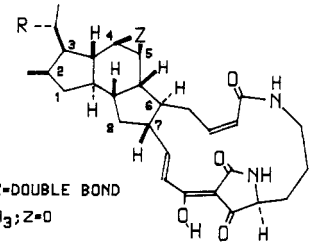
Stereocontrol in the Intramolecular Diels–Alder Reaction. 5. Preparation of a Tetracyclic Intermediate for Ikarugamycin

Summary: The application of the intramolecular Diels–Alder strategy to the construction of a key tetracyclic intermediate **5** is described. Preparation of **5** allows for the control of all eight asymmetric centers present in the carbocyclic segment of ikarugamycin (**1**), an unusual macrocyclic tetramic acid antibiotic. The utility of transition-state selection influenced by preexisting asymmetric centers in the connecting chain was investigated.

Sir: The structure and absolute configuration of (+)-ikarugamycin (**1**), an antiprotozoal antibiotic isolated by Jomon et al.[1] in 1972, was established on the basis of an elegant and carefully executed chemical structure proof by Ito and Hirata.[2] Ikarugamycin (**1**) and the related substance capsimycin (**2**) represent unusual structures, possessing a relatively rare macrocyclic lactam ring fused to a nonterpenoid tricarbocyclic ring system.[3]

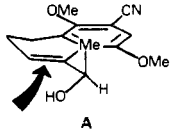


(13) Alternatively, **10** was prepared from **7** by the following sequence of reactions: (i) CuCN/*N*-methylpyrrolidone/150–160 °C/5 h; 97%), (ii) CH_2=CHMgBr (63%), (iii) $Hg(OAc)_2$–$NaBH_4$; Ac_2O–pyridine; aqueous NaOH (23%).

(14) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449–450.

(15) ^1H NMR spectral data (200 MHz, $CDCl_3$). **11**: δ 1.04 (3 H, d, *J* = 6 Hz, C-Me), 2.02 (2 H, m, H-7), 2.70 (1 H, br, OH), 2.75 (1 H, dt, *J* = 18, 7 Hz, H-8), 2.92 (1 H, dt, *J* = 18, 7 Hz, H-8), 3.27 (1 H, br, OH), 3.94 (3 H, s, OMe), 3.99 (3 H, s, OMe), 4.24 (1 H, t, *J* = 5 Hz, H-6), 4.50 (1 H, q, *J* = 6 Hz, H-1′), 4.90 (1 H, br, OH), 6.97 (1 H, s, ArH). **12**: δ 1.05 (3 H, d, *J* = 6 Hz, C-Me), 2.07 (1 H, ddd, *J* = 14, 12, 4 Hz, H-7), 2.42 (1 H, dt, *J* = 14, 4 Hz, H-7), 3.30 (3 H, br, OH), 3.90 (3 H, s, OMe), 4.22 (3 H, s, OMe), 4.91 (1 H, dd, *J* = 12, 4 Hz, H-8), 5.20 (1 H, q, *J* = 6 Hz, H-1′), 5.66 (1 H, t, *J* = 4 Hz, H-6), 7.06 (1 H, s, ArH). **13**: δ 0.86 (3 H, d, *J* = 6 Hz, C-Me), 1.46 (1 H, dt, *J* = 15, 2 Hz, H-7), 2.60 (1 H, d, *J* = 2 Hz, OH), 2.73 (1 H, ddd, *J* = 15, 8, 4 Hz, H-7), 3.77 (1 H, q, *J* = 6 Hz, H-3), 3.95 (3 H, s, OMe), 4.01 (4 H, overlapped OMe and H-8), 5.10 (1 H, dd, *J* = 4, 2 Hz, H-1), 5.73 (1 H, s, OH), 7.10 (1 H, s, ArH).

(16) Cf. the case of 1-(1-hydroxyethyl)-3,4-dihydronaphthalene, which gives a diastereomer ratio of (5*R**,6*R**,1′*R**)/(5*R**,6*R**,1′*S**) = ca. 2:1. The remarkable stereoselectivity observed with **10** could be rationalized by consideration of the preferred conformation A in which a steric interaction between the carbinol side chain and the 4-methoxy group would be minimized. Attack of OsO_4 from the less hindered α-face (arrow) to yield **11** would be highly favorable.



A

(17) Kita, Y.; Haruta, J.; Segawa, J.; Tamura, Y. *Tetrahedron Lett.* **1979**, 4311–4314.

(18) 3*S**-Isomer is expected to show C(3)-Me at δ ca. 1.4.

(19) Jacob, P., III; Callery, P. S.; Shulgin, A. T.; Castagnoli, N., Jr. *J. Org. Chem.* **1976**, *41*, 3627–3629.

(20) Snyder, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1972**, *94*, 227–231.

(21) Kelly, T. R.; Dali, H. M.; Tsang, W.-G. *Tetrahedron Lett.* **1977**, 3859–3860.

(1) Jomon, K.; Kuroda, Y.; Ajisaika, M.; Saki, H. *J. Antibiot.* **1972**, *25*, 271.

(2) (a) Ito, S.; Hirata, Y. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1813. (b) Ito, S.; Hirata, Y. *Ibid.* **1977**, *50*, 227. (c) Ito, S.; Hirata, Y. *Tetrahedron Lett.* **1972**, *1181*. (d) Ito, S.; Hirata, Y. *Ibid.* **1972**, 1185. (e) Ito, S.; Hirata, Y. *Ibid.* **1972**, 2557.

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