related to BF_3·$(OEt)_2$ as an external standard.

$NaBH_4$ was recrystallized from diglyme.[7] The diglyme solutions were standardized prior to use by measuring the amount of hydrogen gas evolved upon hydrolysis in 2 M H_2SO_4. The reproducibility was always within ±2%. The solution was kept under dry nitrogen in storage bottles equipped with Teflon stop cocks and rubber septums. Aliquots were removed by syringe as needed. All glassware was carefully dried to exclude moisture. Isobutyric acid and diglyme were distilled under dry nitrogen prior to use.

Registry No. $NaBH_4$, 16940-66-2; $NaBH_3OCOCHMe_2$, 77979-89-6; $NaBH_2(OCOCHMe_2)_2$, 77979-90-9; $NaBH(OCOCHMe_2)_3$, 77979-91-0; isobutyric acid, 79-31-2.

(7) Brown, H. C.; Mead, E. J.; Subba Rao, B. C. *J. Am. Chem. Soc.* **1955**, *77*, 6209.

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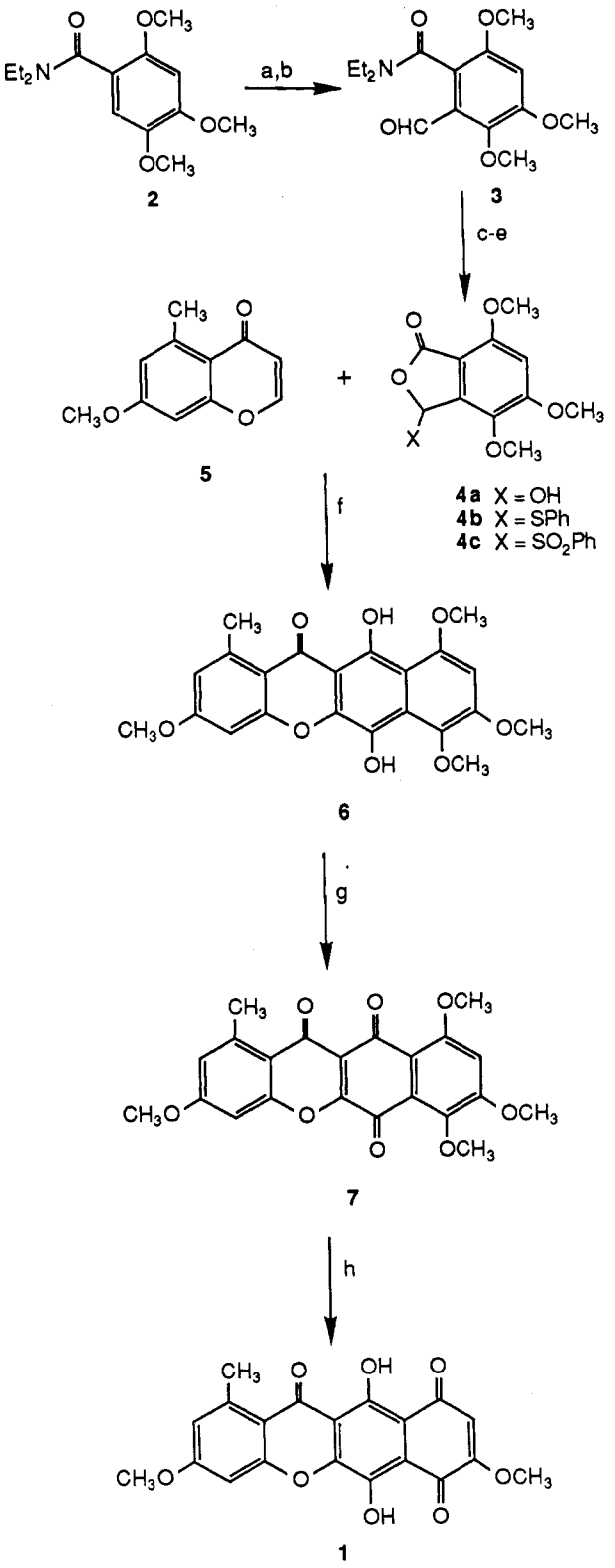
Regiospecific Preparation of the Benz[*b*]xanthen-12-one Ring System: Total Synthesis of Bikaverin

Summary: The benz[*b*]xanthen-12-one ring system can be fabricated regiospecifically through condensation of (phenylsulfonyl)isobenzofuranones with chromones. This discovery was used to achieve a brief synthesis of the antiprotozoal agent bikaverin (1).

Sir: Bikaverin (1), a red pigment with significant and specific antiprotozoal activity, has been isolated from several fungi.[1-5] Although partial assignment of the structure through chemical and spectroscopic studies was possible,[4,6] X-ray analysis was required to establish unambiguously the substitution pattern.[7] Shortly after the structure was elucidated, an elegant regiospecific synthesis of 1 was reported by Barton et al.[8] and more recently two additional preparations have been described.[9,10]

(1) Nakamura, Y.; Shjinomura, T.; Ona, J. *Nippon Ogei* Kagaku **1957**, *31*, 669; *Chem.* Abstr. **1958**, *52*, 17377.
(2) Robinson, P. M.; Park, D.; McClure, W. C. *Trans. Brit. Mycol. Soc.* **1969**, *52*, 447.
(3) Bolan, J.; Fluska, J.; Kuhr, I.; Kuhrova, K. *Folia Microbiol. (Prague)* **1970**, *15*, 479.
(4) Kjer, D.; Pedersen, C.; Bu'Lock, J. D.; Smith, J. R. *J. Chem. Soc. C* **1971**, 2792.
(5) Terashima, N.; Ishida, M.; Hamaski, T.; Hatsuda, Y. *Phytochemistry* **1972**, *11*, 2280.
(6) Cornforth, J. W.; Rybeck, G.; Robinson, P. M.; Park, D. *J. Chem. Soc. C* **1971**, 2786.
(7) de Boer, J. J.; Bright, D.; Dallinga, G.; Hewitt, T. J. *J. Chem. Soc. C* **1971**, 2788.
(8) Barton, D. H. R.; Cottier, L.; Freund, K.; Luini, F.; Magnus, P. D.; Salazar, I. *J. Chem. Soc., Chem. Commun.* **1975**, 699; *J. Chem. Soc., Perkin Trans. 1* **1976**, 499.
(9) Kato, T.; Katagiri, N.; Nakano, J.; Kawamura, H. *J. Chem. Soc., Chem. Commun.* **1977**, 645; *J. Chem. Soc., Perkin Trans. 1* **1981**, 2710.

Scheme I[a]



[a] (a) *sec*-BuLi, TMEDA, THF; (b) DMF, 56%; (c) $H_3O^+Cl^-$, HOAc; 81%; (d) PhSH, catalytic TsOH; 91%; (e) MCPBA, CH_2Cl_2; 100%; (f) LiO-*t*-Bu, THF, −78 °C and reflux; 27%; (g) Ag_2CO_3–Celite; 91%; (h) LiI, DMF; 78%.

Our synthesis of 1, shown in Scheme I, was based on the expectation that condensation of (phenylsulfonyl)isobenzofuranones[11] with chromones would furnish regios-

(10) Kjaer, D.; Kjaer, A.; Risbierg, E. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2815.

0022-3263/88/1953-0223$01.50/0

pecifically benz[b]xanthen-12-ones. The sulfone **4c**, which serves as a synthon for the A and B rings, was prepared from the amide **2**.[12] Lithiation of **2** (*sec*-butyllithium, TMEDA), followed by reaction with DMF, furnished the aldehyde **3** (mp 91–2 °C, lit.[12] mp 92–4 °C; 56%), which was hydrolyzed ($HCl/HOAc/H_2O$) to the phthaldehydic acid **4a** (mp 214–15 °C; 81%). Heating **4a** with benzenethiol in benzene and a catalytic amount of toluenesulfonic acid gave the sulfide **4b** (mp 124–125 °C; 91%), which was oxidized ($MCPBA/CH_2Cl_2$) quantitatively to the sulfone **4c** (mp 175–176 °C).

Condensation of the anion of **4c** with the chromone **5**[13] (LiO-*t*-Bu, THF, −78 °C to room temperature, and then brief reflux) furnished **6** regiospecifically in 27% yield.[14] Oxidation of **6** with Fetizon reagent[15] (Ag_2CO_3/Celite) produced the quinone **7** (91%) with the same physical and spectral properties as those given in the literature. Demethylation of **7** with LiI in DMF[9] (78%) gave bikaverin (**1**), identical[16] with an authentic sample.

The accomplished preparation of **1** is much shorter than those reported previously,[9-11] is achieved in better overall yield, and is amenable to the synthesis of a variety of analogues. The use of chromone as a Michael acceptor expands the utility of the sulfone annelation[1] for regiospecific preparation of polycyclic aromatic ring systems. We are currently utilizing this reaction to prepare other natural products containing a xanthenone fragment.

Acknowledgment. We express our appreciation to Dr. Ryback for providing an authentic sample of Bikaverin. This work was generously supported by the National Cancer Institute of the National Institutes of Health under grant CA 18141.

(11) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. Condensation of (phenylsulfonyl)isobenzofuranones has been widely used by us and by others to achieve regiospecific total syntheses of naturally occurring polycyclic aromatic systems. For an extensive list, see ref 9 in: Hauser, F. M.; Baghdanov, V. M. *Tetrahedron* **1984**, *80*, 4719.

(12) Parker, K. A.; Spero, D. M.; Koziski, K. A. *J. Org. Chem.* **1987**, *52*, 183.

(13) The chromone **5** was prepared by sodium hydride condensation of 2-hydroxy-4-methoxy-6-methylacetophenone with ethyl formate. The diketone intermediate was cyclized to the chromone with trifluoroacetic acid and trifluoroacetic anhydride. For a similar preparation, see: Ahlumalia, V. K.; Chanandra, P. *Indian J. Chem.* **1977**, *15b*, 331.

(14) Much better yields of benz[b]xanthen-12-ones are obtained from condensation of less highly substituted (phenylsulfonyl)isobenzofuranones and chromones. For example, condensation of chromone with 7-methoxy-3-(phenylsulfonyl)-1(3*H*)-isobenzofuranone gave the corresponding methoxybenzxanthen-12-one in 65% yield.

(15) Fetizon, M.; Golfier, M. *C. R. Seances Acad. Sci.* **1968**, *267*, 900.

(16) The infrared and ^1H NMR spectral properties of the synthetic and authentic materials were identical.

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Ruthenium(IV) Dioxide in Fluoro Acid Medium: An Efficient Biaryl Phenol Coupling Process, Exemplified with a Biomimetic Access to the Skeleton of Steganacin from Presteganes[1,2]

Summary: Ruthenium(IV) dioxide dihydrate in fluoro acids was found to be very efficient for the oxidative phenol coupling of presteganes **1a** and **1b** to give the corresponding bisbenzocyclooctadiene lactones **2a** and **2b**, closely related to the antitumor lignan steganacin. The same conditions applied to the mammalian lignan enterolactone **1e** were ineffective. Ultrasound assistance and use of the triflic acid–triflic anhydride–boron trifluoride medium at room temperature were found to be the best conditions.

Sir: Bridged biaryls related to the well-known classes of natural products of high pharmaceutical interest are widely distributed in higher plants.[3] Their biogenesis always involves enzymic intramolecular biaryl oxidative coupling of phenolic precursors via radical cations, as a key step (Scheme I). So, an improvement of both the efficiency and selectivity of the biomimetic synthetic methods providing access to these skeletons would be very useful.

Kupchan[4] and, more recently, Taylor and McKillop[5] have improved the sluggish known methods[6] by using vanadium(V) oxyhalides and thallium(III) tris(trifluoroacetate) (TTFA), respectively. Unfortunately, the yield of phenolic coupling, which is the real mechanism used by nature, generally remains poor to medium in the laboratory.

As a part of our continuing work in the isolation and the synthesis of potential antitumor and antiviral drugs, effort was devoted to the development of an efficient route to the above mentioned classes of natural substances. Recently we described that ruthenium(IV) dioxide in TFA–TFAA medium is a versatile reagent for the synthesis of bridged biaryls from *nonphenolic* precursors.[7] In the present work, we attempted to determine whether the title reagent could be employed for an efficient biomimetic synthesis of bisbenzocyclooctadiene lactones closely related to the antitumor lignan steganacin by oxidative coupling

(1) Presented at the 30th National Organic Symposium of the American Chemical Society, Vancouver, June 22, 1987. The present paper is dedicated to the late S. M. Kupchan.

(2) Part of thesis of Y. L.

(3) Including the following. (a) **Alkaloids.** Antitumor aporphines, e.g., thalicarpine: Hussain, S. F.; Freyer, A. J.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod.* **1986**, *49*, 494. Homoaporphines: Castro, J. L.; Castedo, L.; Riguera, R. *Tetrahedron Lett.* **1985**, *26*, 1561. Azahomoaporphines: Cassels, B. K.; Cavé, A.; Davoust, D.; Hocquemiller, R.; Rasamizafy, S.; Tadic, D. *J. Chem. Soc., Chem. Commun.* **1986**, 1481. Antitumor phenanthroquinolizidines, e.g., cryptopleurine: Iida, H.; Watanabe, Y.; Tanaka, M.; Kibayashi, C. *J. Org. Chem.* **1984**, *49*, 2412. Antiviral phenanthroindolizidines, e.g., tylophorine: Gellert, E. *J. Nat. Prod.* **1982**, *45*, 50. Dibenzazecines: Aladesanmi, A. J.; Kelley, C. J.; Leary, J. D. *J. Nat. Prod.* **1983**, *46*, 127. Dibenzazonines: Kupchan, S. M.; Kim, C. K. *J. Am. Chem. Soc.* **1975**, *97*, 5623. Antitumor tropolones, e.g., Colchicine: Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4594. Antitumor benzodihydrophenanthridines, e.g., nitidine: Zee-Cheng, R. K. I.; Cheng, C. C. *J. Med. Chem.* **1975**, *18*, 66. (b) **Lignoids.** Dimethylbisbenzocyclooctadienes, e.g., schizandrins: Takeya, T.; Okubo, T.; Nishida, S.; Tobinaga, S. *Chem. Pharm. Bull.* **1985**, *33*, 3599. Bisbenzocyclooctadiene lactones, e.g., steganacin: Kupchan, S. M.; Britton, R. W.; Ziegler, M. F.; Gilmore, C. J.; Restivo, R. V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 335. Robin, J.-P.; Davoust, D.; Taafrout, M. *Tetrahedron Lett.* **1986**, *27*, 2871. (c) **Dihydrophenanthrenes.** Cytotoxic juncusol: Kende, A. S.; Curran, D. P. *Tetrahedron Lett.* **1978**, *33*, 3003.

(4) Kupchan, S. M.; Liepa, A. J.; Kameswaran, V.; Bryan, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 6861.

(5) Taylor, E. C.; Andrade, J. G.; Rall, G. J. H.; McKillop, A. *J. Am. Chem. Soc.* **1980**, *102*, 6513.

(6) (a) For a review on phenol coupling, see: Taylor, W. I.; Battersby, A. R. "Oxidative Coupling of Phenols"; Marcel Dekker: New York, 1967. (b) For an exhaustive recent review on radical ion biaryl coupling, see: Kovacic, P.; Jones, M. B. *Chem. Rev.* **1987**, *87*, 357 and reviews cited herein (including Lewis acid–oxidant combinations, phenolic coupling, intramolecular couplings, and so on).

(7) Including (a) Lignans pertaining to the steganacin group: Landais, Y.; Robin, J. P. *Tetrahedron Lett.* **1986**, *27*, 1785. (b) Neolignans of the schizandrin group: Landais, Y.; Lebrun, A.; Robin, J. P. *Tetrahedron Lett.* **1986**, *27*, 5377. (c) Aporphinic, homoaporphinic, and azafluoranthene alkaloids: Landais, Y.; Rambault, D.; Robin, J. P. *Tetrahedron Lett.* **1987**, *28*, 543 and references cited herein.

0022-3263/88/1953-0224$01.50/0