Communications

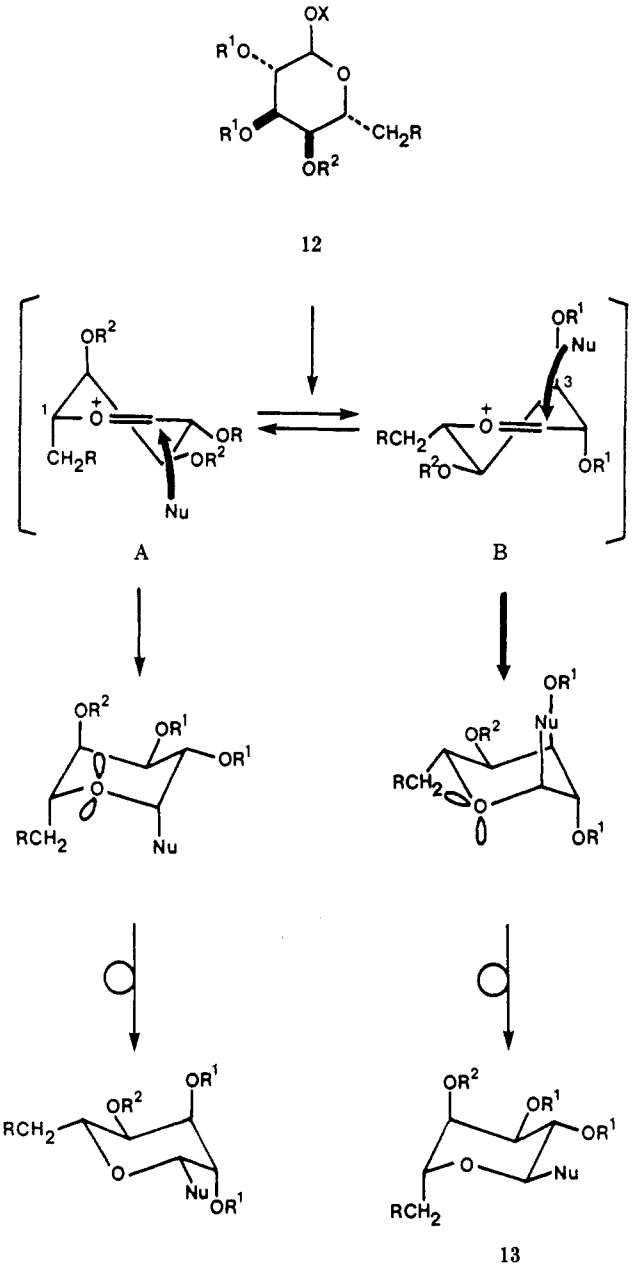
Synthesis of C-Disaccharides

Summary: Stereocontrolled syntheses of four C-disaccharides **10**, **11**, **16**, and **17** were reported. The $(n\text{-Pr})_3SiH/BF_3{\cdot}Et_2O$ reduction of hemiketals such as **7** yielded the equatorially substituted C-glycoside as the major product while C-alkylation $(CH{\equiv}CCH_2Si(CH_3)_3/BF_3{\cdot}Et_2O)$ of **12** gave the axially substituted C-glycoside as the major product.

Sir: In connection with the structural and synthetic studies on the marine natural product palytoxin,[1-3] we became interested in comparing the conformational preference of glycosides with that of the corresponding C-glycosides.[4] Along this line, we were curious to examine the conformational behavior of the carbon analogues of disaccharides such as cellobiose and maltose. In this communication, we would like to report the chemical synthesis of requisite C-disaccharides.[5]

Wittig reaction of the ylide generated from **1**[6,7] with **2**[8] (*n*-BuLi/THF/0 °C, followed by addition of the aldehyde at −78 °C) gave exclusively the *cis*-olefin **3** (82% yield; α_D −38.5°). Osmylation of **3** (OsO_4/py/THF/−40 °C) yielded a 6:1 mixture of the expected diols, which were separated by silica gel chromatography (Chromatotron/1:1 EtOAc–hexanes) to give **4** (60% yield; α_D −16.0°) and **5** (11% yield; α_D −18.5°). On the basis of the empirical rule,[9] the stereochemistry of **4** and **5** was tentatively assigned as indicated, which was confirmed later (vide infra). Selective protection of **4** was conveniently achieved by treatment with *p*-methoxybenzyl bromide (3 equiv of RBr/NaH/THF/rt)[10] to provide the mono-*p*-methoxybenzyl ether **6** (69% direct and 86% twice-recycled[11] yields; α_D −11.0°).

Scheme I



(1) For the gross structure of palytoxin, see: (a) Uemura, D.; Ueda, K.; Hirata, Y.; Naoki, H.; Iwashita, T. *Tetrahedron Lett.* **1981**, *22*, 2781 and references cited therein. (b) Moore, R. E.; Bartolini, G. *J. Am. Chem. Soc.* **1981**, *103*, 2491 and references cited therein. For the structures of minor constituents, see: Uemura, D.; Hirata, Y.; Iwashita, T.; Naoki, H. *Tetrahedron* **1985**, *41*, 1007.

(2) For the stereochemistry assignment primarily based on organic synthesis, see: Cha, J. K.; Christ, W. J.; Finan, J. M.; Fujioka, H.; Kishi, Y.; Klein, L. L.; Ko, S. S.; Leder, J.; McWhorter, W. W., Jr.; Pfaff, K.-P.; Yonaga, M.; Uemura, D.; Hirata, Y. *J. Am. Chem. Soc.* **1982**, *104*, 7369 and preceding papers. For the stereochemistry assignment primarily based on spectroscopic methods, see: Moore, R. E.; Bartolini, G.; Barchi, J.; Bothner-By, A. A.; Dadok, J.; Ford, J. *J. Am. Chem. Soc.* **1982**, *104*, 3776.

(3) For synthetic studies on palytoxin, see: (a) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644 and references cited therein. (b) Still, W. C.; Galynker, I. *J. Am. Chem. Soc.* **1982**, *104*, 1774.

(4) Wu, T. C.; Kishi, Y., submitted for publication.

(5) For the synthesis of C-disaccharides, see: (a) Rouzaud, D.; Sinay, P. *J. Chem. Soc., Chem. Commun.* **1983**, 1353. (b) Giese, B.; Witzel, T. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 450.

(6) This substance was prepared in seven steps [(1) NaOMe/MeOH/rt; (2) KOAc/AcOH/Δ, followed by NaOMe/MeOH workup; (3) $PhCH_2Br$/NaH/DMF–THF/rt; (4) OsO_4/*N*-methylmorpholine *N*-oxide/aqueous acetone/rt, followed by $NaIO_4$/50% aqueous MeOH and then $NaBH_4$/EtOH workup; (5) MsCl/Et_3N/Et_2O/rt; (6) NaI/acetone-/rt; (7) $(Ph)_3P$/DMF/110 °C] in 43% overall yield from 1,6-anhydro-4-deoxy-4-(2-propenyl)-β-D-glucopyranose 2-(4-toluenesulfonate): Kelly, A. G.; Roberts, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 228.

(7) Satisfactory spectroscopic data were obtained for all the new compounds reported in this paper. The α_D values were taken in $CHCl_3$ with approximately c = 1.0 except for C-disaccharides **10**, **11**, **16**, and **17**.

(8) This substance was prepared from D-arabinose following the procedure used for the synthesis of its antipode: Just, G.; Potvin, P. *Can. J. Chem.* **1980**, *58*, 2173.

(9) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247 and references cited therein.

(10) The procedure for the selective monoprotection was originally developed by Dr. Hon in our laboratory on a system similar to **4**.

(11) Under these conditions a mixture of the desired monoprotected product (66%), the bisprotected product (19%), and the undesired monoprotected product (8%) in addition to the starting material (5%) was observed. Deprotection (CAN/H_2O/MeCN/0 °C) of the bisprotected and undesired monoprotected products yielded the starting material (82% yield), which was recycled.

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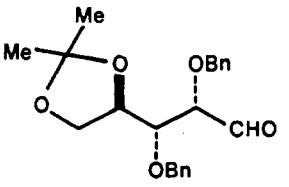
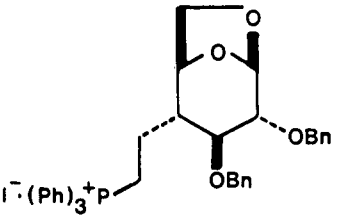
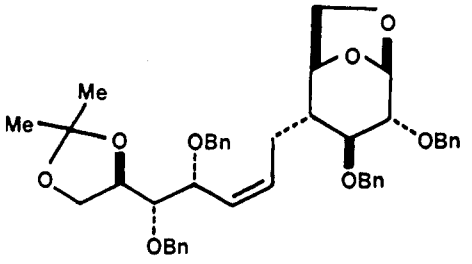


2



1



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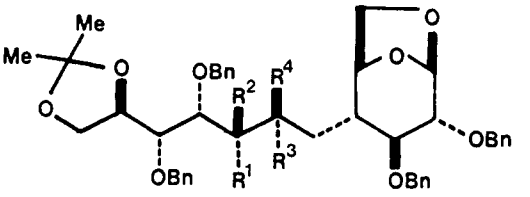
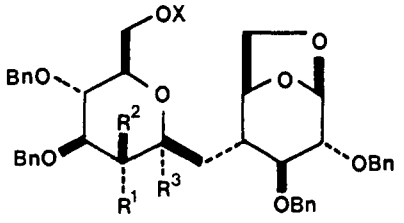
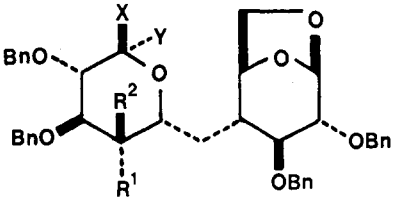


4: $R^1 = R^4 = H$, $R^2 = R^3 = OH$
5: $R^1 = R^4 = OH$, $R^2 = R^3 = H$
6: $R^1 = R^4 = H$, $R^2 = p$-$MeOPhCH_2O$, $R^3 = OH$



7:[12] X = Bz, $R^1 = H$, $R^2 = p$-$MeOPhCH_2O$, $R^3 = OH$
8: X = Bz, $R^1 = H$, $R^2 = OH$, $R^3 = H$
9: X = Bz, $R^1 = OH$, $R^2 = H$, $R^3 = H$



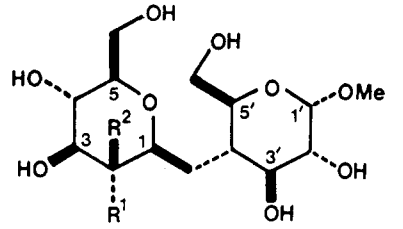
12α:[19] X = H, Y = O-PNB, $R^1 = H$, $R^2 = p$-$MeOPhCH_2O$
12β:[19] X = O-PNB, Y = H, $R^1 = H$, $R^2 = p$-$MeOPhCH_2O$

13: X = CH=C=CH_2, Y = H, $R^1 = H$, $R^2 = OH$
14: X = CH_2OH, Y = H, $R^1 = H$, $R^2 = OH$
15: X = CH_2OBz, Y = H, $R^1 = OH$, $R^2 = H$

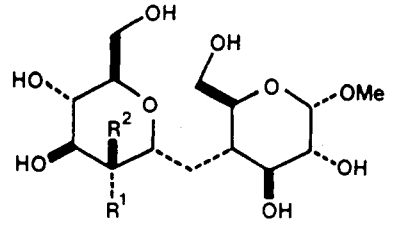
Although we still need to examine more examples to draw a firm conclusion, the observed selectivity between the two hydroxyl moieties in this type of arrangement seems to be general and useful from a preparative point of view. We feel that the electronic effect of the adjacent carbon–oxygen bond plays an important role in the observed reactivity difference.

The mono-*p*-methoxybenzyl ether **6** was then transformed into the hemiketal **7**[12] in 75% overall yield in three steps, i.e., (1) Swern oxidation,[13] (2) acetonide hydrolysis (4 N HCl/THF/rt), and (3) benzoylation (3 equiv of $PhCOCl/py/CH_2Cl_2$/rt). Based on our previous experience,[14] we anticipated that silane reduction of **7** in an acidic medium should preferentially yield the equatorially substituted *C*-glycoside; indeed, **7** gave the equatorial product **8** (82% yield; α_D −13.9°) along with a small amount of its axial isomer (the stereoselectivity = 7:1) under the conditions of $(n\text{-}Pr)_3SiH/BF_3\cdot Et_2O/CH_3CN/-20$ °C.[15] The ^1H NMR spectrum of **8** was fully consistent with the assigned structure.

Exact parallel experiments starting with the minor diol **5** furnished the gluco product **9** (α_D +2.6°). It is interesting to note that the silane reduction of the hemiketal in the gluco series gave exclusively the equatorial product **9**. The



10: $R^1 = H$, $R^2 = OH$
11: $R^1 = OH$, $R^2 = H$



16: $R^1 = H$, $R^2 = OH$
17: $R^1 = OH$, $R^2 = H$

^1H NMR spectrum of **9** clearly showed $J_{1,2}$ = 9.4 Hz, which confirmed the tentatively assigned stereochemistry of **4**

(12) This substance was isolated as a mixture of α- and β-ketols.
(13) (a) Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651. (b) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(14) Lewis, M. D.; Cha, J. K.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976. For a recent paper on this subject, see: Giannis, A.; Sandhoff, K. *Tetrahedron Lett.* **1985**, *26*, 1479 and references cited therein.
(15) The stereoselectivity of this reduction depended delicately upon silanes; for example, $(Et)_3SiH$, $(Ph)(Me)_2SiH$, and $(Me)(Ph)_2SiH$ yielded a 3:1, 3:2, and 3:2 mixture of the equatorial and axial isomers, respectively.

and **5**. Transformation of **8** (manno series) into **9** (gluco series) was also feasible in two steps, i.e., (1) Swern oxidation and (2) BH_3·$(Et)_3N$ reduction, in excellent overall yield; the stereoselectivity of the reduction was greater than 8:1 in favor of the gluco series.[16]

After deprotection [H_2/Pd(OH)$_2$ on C/MeOH/rt], **8** and **9** were subjected to methanolysis under acidic conditions (HCl/MeOH/90 °C) to yield **10**[17] (90% overall yield; α_D in MeOH +38.9°) and **11**[17] (90% overall yield; α_D in MeOH +63.2°), respectively. The assigned structures **10** and **11** were fully consistent with the spectroscopic data; in particular, the ^{1}H NMR spectrum provided conclusive evidence for the stereochemistry assigned.[18]

The axially substituted *C*-glycosides **16** and **17** were also synthesized from **6**. Thus, **6** was transformed into the *p*-nitrobenzoates **12α**[19] (51% overall yield; α_D +31.0°) and **12β**[19] (46% overall yield; α_D −18.3°) in three steps, i.e., (1) AcOH–H_2O (6:4)/40 °C, (2) $Pb(OAc)_4/C_6H_6$/O °C, and (3) p-$O_2NC_6H_4COCl$/py/CH_2Cl_2/rt. Based on the following considerations, we anticipated that the desired C-glycosidation would preferentially occur from the oxonium ion generated from **12α,β** under acidic conditions (Scheme I). First, a nucleophilic attack on the conformers A and B of the oxonium ion leading to the chair-like transition state should be more favorable than one leading to a boat-like transition state. Second, nucleophilic attack on conformer A should be slower than that on conformer B, since the C(1)-CH_2R group of A would cause a more serious steric interaction for the incoming nucleophile than the C(3)-OCH_2Ph group of B. Third, the product that resulted from an axial attack on the conformer B would flip over to the alternative chair conformation to yield the desired C(1)-axially substituted *C*-glycoside. Treatment of **12β** with $CH{\equiv}CCH_2Si(CH_3)_3$ in CH_3CN containing BF_3·Et_2O[20] yielded the anticipated product **13** (70% yield; α_D −1.8°) along with a small amount of the equatorial isomer (the stereoselectivity = ca. 10:1). However, the stereoisomer **12α** was recovered unchanged under the same conditions. Under more forcing conditions, the 1,6-anhydroglucose moiety participated also in the C-alkylation reaction. Thus, it was more practical to transform **12α** to **12β**,[21] followed by C-alkylation.

Ozonolysis (O_3/MeOH/−78 °C), followed by reduction ($NaBH_4$/EtOH/O °C), furnished the diol **14** (92% overall yield; α_D −8.4°), which was transformed into the methyl glycoside **16**[17,18] (α_D in MeOH +83.4°) in 90% overall yield in two steps [(1) H_2/Pd(OH)$_2$ on C/MeOH/rt and (2) HCl/MeOH/90 °C]. The corresponding gluco product was also obtained from **14**; protection of the primary alcohol [PhCOCl/py/CH_2Cl_2/rt], Swern oxidation, and reduction of the resultant ketone (BH_3·THF/THF/O °C)[22] yielded **15** (80% overall yield; α_D +8.1°) along with a small amount of the corresponding manno product (the stereoselectivity = 18:1). Transformation of **15** into the gluco methyl glycoside **17**[17,18] (α_D in MeOH +53.3°) was performed in 90% overall yield utilizing the same sequence of reactions as **14** to **16**.

The methods outlined herein should be flexible enough to synthesize a variety of the carbon analogues of disaccharides with α- and β-glycoside bonds. Investigations along this line, as well as the conformational studies of these *C*-disaccharides, will be reported elsewhere.

Acknowledgment. Financial support from the National Institutes of Health (NS 12108) is gratefully acknowledged. NMR spectrometers used in this research were funded by NSF Grant (CHE-84-10774) and NIH Shared Instrumentation Program (1 S10 RR01748).

Registry No. **1**, 106929-08-2; **2**, 106929-09-3; **3**, 106929-10-6; **4**, 106929-11-7; **5**, 106974-26-9; **6**, 106929-12-8; **7**, 106929-13-9; **8**, 106929-14-0; **9**, 106974-27-0; **10**, 106929-15-1; **11**, 107032-98-4; **12α**, 106929-16-2; **12β**, 106974-28-1; **13**, 106929-17-3; **14**, 106929-18-4; **15**, 106974-30-5; **16**, 106974-29-2; **17**, 106974-31-6; $CH{\equiv}CCH_2Si(CH_3)_3$, 13361-64-3.

Supplementary Material Available: ^{1}H NMR spectra of *C*-disaccharides **10**, **11**, **16**, and **17**, and key intermediates (8 pages). Ordering information is given on any current masthead page.

(16) BH_3·THF reduction of this substrate gave a 3:2 mixture of the gluco and manno products (see ref 22).

(17) Under the methanolysis conditions, an approximately 5:1 mixture of the axial and equatorial methyl glycosides were formed. Analytically pure axial methyl glycosides were obtained by acetylation (Ac_2O/py), chromatographic separation, and base hydrolysis (aqueous NaOH).

(18) The ^{1}H NMR spectrum of **10**, **11**, **16**, and **17** was recorded on a Bruker AM 500 spectrometer (500 MHz) in CD_3OD. The following spin–spin coupling constants were observed. **10**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.3, $J_{3',4'}$ = 10.2, $J_{4',5'}$ = 10.1, $J_{5',6'}$ = 1.8 and 5.3, $J_{6',6'}$ = 11.8, $J_{4',A}$ = 5.2, $J_{4',B}$ = 3.8, $J_{A,B}$ = 14.1, $J_{1,A}$ = 8.8, $J_{1,B}$ = 3.2, $J_{1,2}$ < 1.0, $J_{2,3}$ = 2.2, $J_{3,4}$ = 9.4, $J_{4,5}$ = 8.9, $J_{5,6}$ = 2.3 and 6.7, and $J_{6,6}$ = 11.6. **11**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.3, $J_{3',4'}$ = 10.3, $J_{4',5'}$ = 10.9, $J_{5',6'}$ = 1.7 and 5.4, $J_{6',6'}$ = 11.8, $J_{4',A}$ = 3.5, $J_{4',B}$ = 4.7, $J_{A,B}$ = 15.3, $J_{1,A}$ = 9.2, $J_{1,B}$ = 1.7, $J_{1,2}$ = 9.2, $J_{2,3}$ = 9.1, $J_{3,4}$ = 9.7, $J_{4,5}$ = 8.7, $J_{5,6}$ = 2.4 and 5.2, and $J_{6,6}$ = 11.8. **16**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.4, $J_{3',4'}$ = 10.8, $J_{4',5'}$ = 11.3, $J_{5',6'}$ = 2.4 and 6.4, $J_{6',6'}$ = 11.6, $J_{4',A}$ = 3.3, $J_{4',B}$ = 5.5, $J_{A,B}$ = 14.4, $J_{1,A}$ = 9.2, $J_{1,B}$ = 4.6, $J_{1,2}$ = 3.7, $J_{2,3}$ = 2.5, $J_{3,4}$ = 9.8, $J_{4,5}$ = 7.6, $J_{5,6}$ = 3.8 and 7.0, and $J_{6,6}$ = 11.3. **17**: $J_{1',2'}$ = 3.7 Hz, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 10.6, $J_{4',5'}$ = 8.8, $J_{5',6'}$ = 2.3 and 4.9, $J_{6',6'}$ = 12.0, $J_{4',A}$ = 2.7, $J_{4',B}$ = 5.5, $J_{A,B}$ = 14.8, $J_{1,A}$ = 10.1, $J_{1,B}$ = 3.1, $J_{1,2}$ = 9.2, $J_{2,3}$ = 9.2, $J_{3,4}$ = 8.4, $J_{4,5}$ = 8.8, $J_{5,6}$ = 2.7 and 4.6, and $J_{6,6}$ = 12.3.

(19) We were unable to establish the stereochemistry of **12α** and **12β** firmly based on the NMR spectra. However, the reactivity difference observed in the alkylation of **12α** and **12β** strongly suggests the stereochemistry assignment as indicated.

(20) Wu, T. C.; Kishi, Y., unpublished results.

(21) Base hydrolysis (K_2CO_3/MeOH/rt) and *p*-nitrobenzoylation (p-$NO_2C_6H_4COCl$/py/CH_2Cl_2/rt) yielded approximately a 1:2 mixture of **12α** and **12β** in 75–80% yield.

(22) Garegg, P. J.; Maron, L. *Acta Chem. Scand., Ser. B* **1979**, *33B*, 453.

Stefan A. Babirad, Yuan Wang, Yoshito Kishi*
Department of Chemistry
Harvard University
Cambridge, Massachusetts 02138
Received November 10, 1986

A New Approach to the Total Synthesis of Pseudomonic Acid C

Summary: The glycolate ester enolate Claisen rearrangement was used to introduce the side chain stereochemistry in a synthesis of pseudomonic acid C.

Sir: Pseudomonic acid C (**1c**) is a member of a family of *C*-pyranoside antibacterials which have been isolated from fermentations of a strain of *Pseudomonas fluorescens*.[1] Notwithstanding a narrow range of activity constrained mainly to gram-positive bacteria,[2] their good activity against various skin pathogens[3] combined with a novel and challenging structure have made them inviting targets for

(1) (a) Pseudomonic acid A: Banks, G. T.; Barrow, K.; Chain, E. B.; Fuller, A. T.; Mellows, G.; Woolford, M. *Nature (London)* **1971**, *234*, 416. (b) Pseudomonic acid B: Chain, E. B.; Mellow, G. *J. Chem. Soc., Chem. Commun.* **1977**, 318. (c) Pseudomonic acid C: Clayton, J. P.; O'Hanlon, P. J.; Rogers, N. H. *Tetrahedron Lett.* **1980**, *21*, 881. (d) Pseudomonic acid D: O'Hanlon, P. J.; Rogers, N. H.; Tyler, J. W. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2655.

(2) (a) White, A. R.; Masters, P. J.; Sutherland, R. *Proc. Int. Congr. Chemother.*, **1983**, *3*, 4.6/7-24. (b) Tasker, T. C. G.; Boon, R. J.; Masters, P. J.; King, J. D. *Ibid.* **1983**, *3*, 4.6/7-25.

(3) (a) Reid, J.; Cooper, D. L. *Proc. Int. Congr. Chemother., 13th* **1983**, *3*, 4.6/7-26. (b) Davies, B. I.; Wuite, J.; Go, M.; Lambers, J. *Ibid.* **1983**, *3*, 4.6/7-27.

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