

## Differential Use of the Pyranoside Ring for Stereocontrolled Routes to Triquinanes: Silphinene and Silhiperfolene Skeleta

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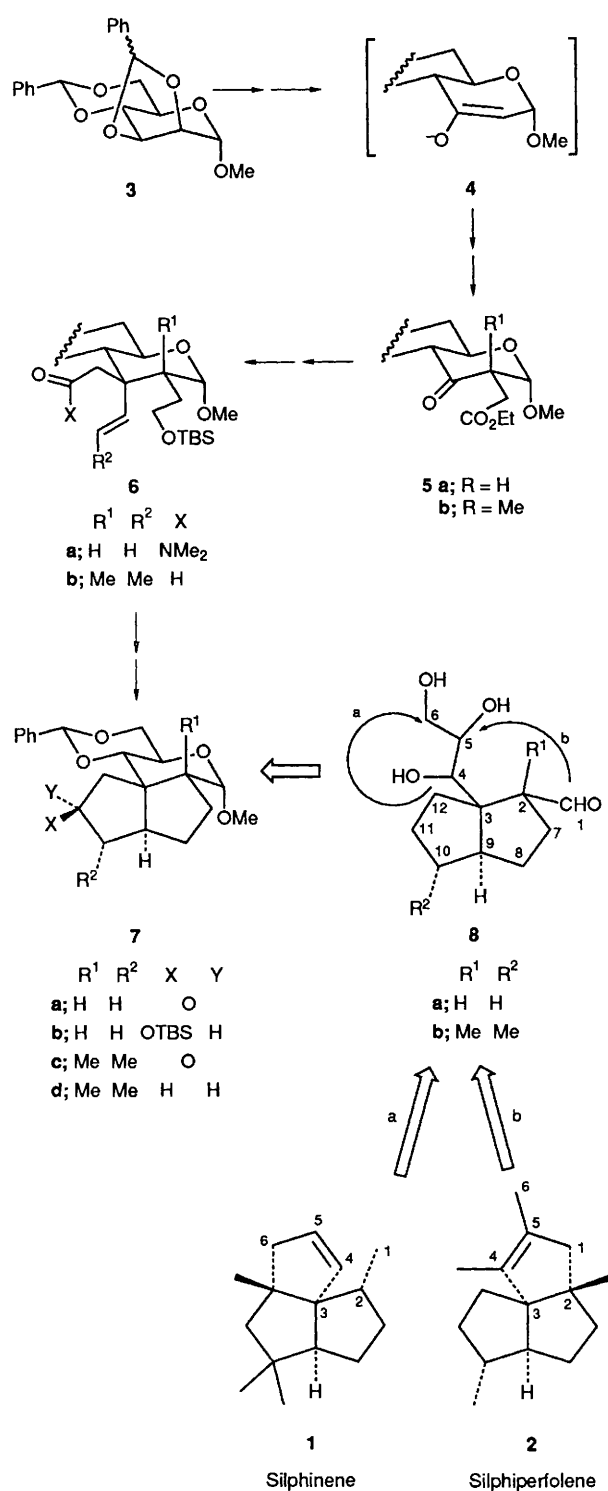
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The use of the pyranosidodiquinane **7** as a key intermediate for constructing the skeleta of **1** and **2** involving a procedure in which all of the stereochemistry is established at the level of **7** before the sugar residue is utilized to obtain this ring.

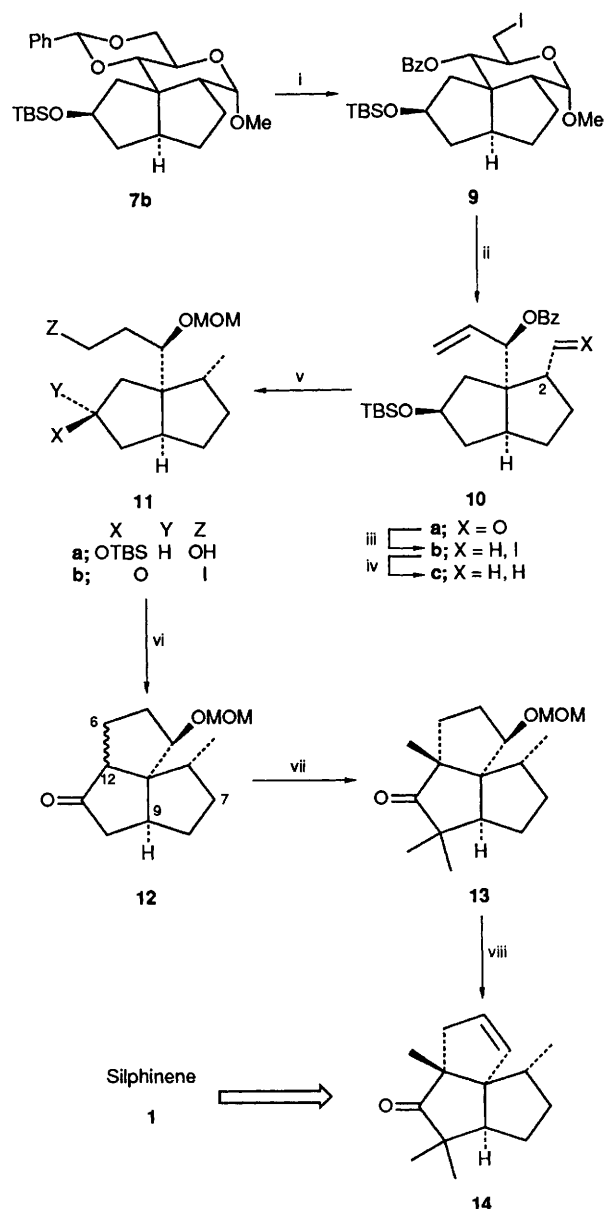
Carbohydrate to carbocycle transformations offer routes to a large variety of optically active natural products.<sup>1</sup> For the carbohydrate-based routes to complex polyquinanes currently being developed in our laboratory,<sup>2</sup> we have sought to establish and verify all stereocentres of the target molecules while the pyranosidic moiety is still intact. This strategy requires that the targets, exemplified here by the angularly fused triquinanes silphinene<sup>3</sup> **1** and silhiperfolene<sup>4</sup> **2** be

presented in such a way that all (crucial) stereocentres are made to coincide with the pyranosidodiquinane precursor.

In order to realize this objective, we rely upon the unique characteristics of the pyranosidic enolate **4**<sup>5</sup> the electronic features of which confer unusual resistance of the anomeric methoxy group towards  $\beta$ -elimination, a direct result of which is the fact that the multiple branches in **5** and **6** can be elaborated with complete stereoselectivity.<sup>6</sup> Thus, although

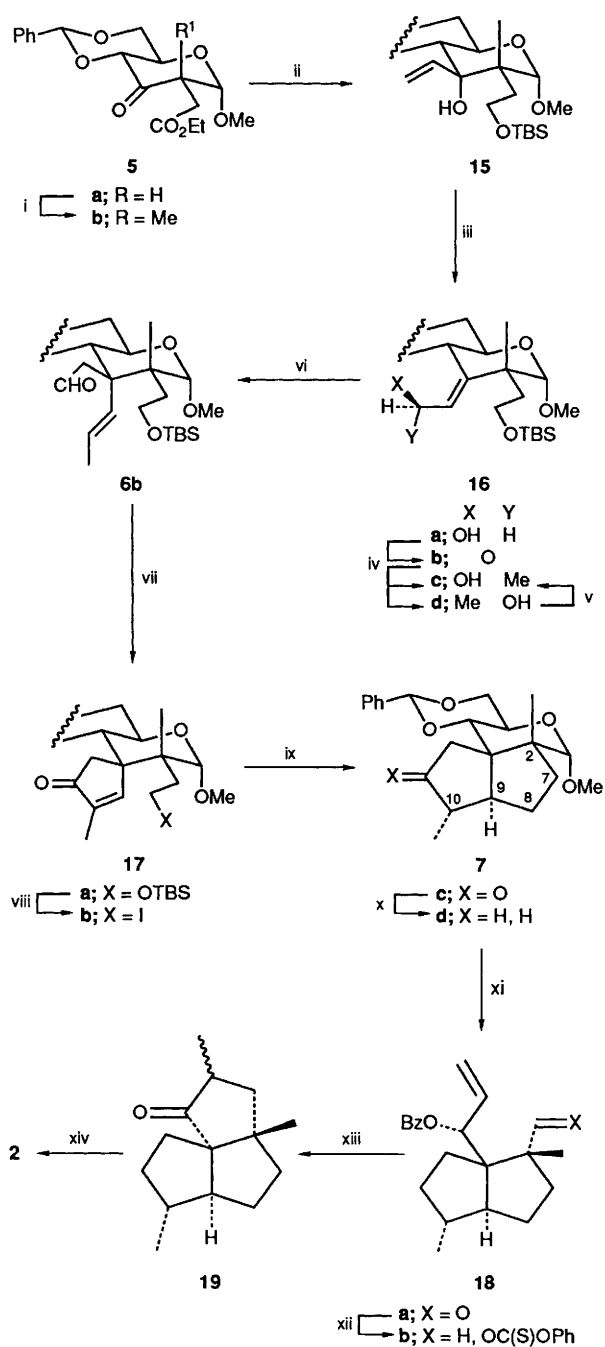


the C-2 and C-3 stereocentres of the original sugar **3**, are destroyed in **4** our methodology is rewarded with much richer functionalization in stereochemically pure **6**. In this manuscript we illustrate our approach in which all six carbons of the sugar **3** are preserved in the targets, having been used either for stereocontrol or functionalization.



**Scheme 2** Reagents and conditions: (i) (a) NBS/BaCO<sub>3</sub>/CCl<sub>4</sub>/reflux 0.5 h; (b) NaI/MeCOEt/reflux, 18 h (84%). (ii) Zn(Hg)/EtOH/reflux, 2 h (81%). (iii) NaBH<sub>4</sub>/MeOH/5 min (92%). (iv) NaBH<sub>4</sub>/DMF/16 h (85%). (v) (a) BH<sub>3</sub>·THF/NaOH/H<sub>2</sub>O<sub>2</sub>; (b) Ph<sub>3</sub>P/I<sub>2</sub>/C<sub>6</sub>H<sub>6</sub> (82%). (vi) (a) HOAc/H<sub>2</sub>O/THF; (b) PCC/CH<sub>2</sub>Cl<sub>2</sub>; (c) tBuOK/tBuOH/THF (75%). (vii) LiN(SiMe<sub>3</sub>)<sub>2</sub>/MeI/THF/0 °C → room temp./5 h (10%). (viii) (a) 6 M HCl/THF; (b) PhOC(S)Cl/CH<sub>2</sub>Cl<sub>2</sub>; (c) triisopropylbenzene/reflux/45 min (50%)

The relationship between the previously described pyranosidodiquinane **7a**,<sup>2a</sup> silphinene **1**, and silhiperfolene **2**, is evident from Scheme 1. The methyl substitution patterns would be developed at some stage prior to **7**, and subsequent opening of the pyranoside ring would then give the synthon **8**. For the silphinene skeleton, the aldehyde group of **8a** would have to be deoxygenated, and the third ring would require bond formation between C-12 and C-6. In view of the *cis* fusion expected in the latter reaction, subsequent entry of the angular C-12-CH<sub>3</sub> of **1** would necessarily occur from the *exo*



**Scheme 3** Reagents and conditions: (i)  $\text{KH/MeI/THF}$  (78%); (ii) (a)  $\text{CH}_2=\text{CHMgBr/THF/20 min}$ ; (b)  $\text{LiAlH}_4/\text{THF}/0^\circ\text{C}$  45 min; (c)  $\text{Bu-Me}_2\text{SiCl/imidazole/THF}$  (73%); (iii) (a)  $\text{SOCl}_2/\text{pyridine/THF}/0^\circ\text{C}$  1 h; (b)  $\text{KOAc/DMF}$  then  $\text{NaOMe/MeOH}$  (62%); (iv) (a)  $\text{PCC/CH}_2\text{Cl}_2$ ; (b)  $\text{MeMgCl/THF}$  (83%) (**16c** + **16d**); (v) (a)  $\text{Ph}_3\text{P/PhCOOH/DEAD/THF}$ ; (b)  $\text{MeLi/Et}_2\text{O}$  (78%); (vi) (a)  $\text{CH}_2=\text{CHOEt/Hg}(\text{OCOCF}_3)_2/\text{Et}_2\text{O}/12 \text{ h}$  then xylene/reflux 24 h (78%); (vii) (a)  $\text{EtMgBr/THF}$ ; (b)  $(\text{COCl})_2/\text{DMSO/CH}_2\text{Cl}_2$ ; (c)  $\text{O}_3/\text{MeOH/CH}_2\text{Cl}_2$ ; (d)  $\text{Bu}^t\text{OK/THF}$  (45%); (viii) (a)  $\text{Bu}_4\text{NF/THF}$ ; (b)  $\text{Ph}_3\text{P/I}_2/\text{PhH}$  (77%); (ix)  $\text{Bu}_3\text{SnH/PhH}$  (81%); (x) (a)  $\text{LiN}(\text{SiMe}_3)_2/\text{PhN}(\text{SO}_2\text{CF}_3)_2/\text{THF}$ ; (b)  $\text{H}_2/\text{Pd/EtOH}$  (52%); (xi) (a)  $\text{NBS/BaCO}_3/\text{CCl}_4/\text{reflux}$  0.5 h; (b)  $\text{NaI/MeCOEt/reflux}$  18 h; (c)  $\text{Zn(Hg)/EtOH/reflux}$  2 h (82%); (xii) (a)  $\text{NaBH}_4/\text{MeOH/room temp.}$  5 min; (b)  $\text{PhOC(S)Cl/DMAP/CH}_2\text{Cl}_2$  (96%); (xiii) (a)  $\text{Bu}_3\text{SnH/PhH}$ ; (b)  $\text{LiAlH}_4/\text{Et}_2\text{O}/0^\circ\text{C}$  30 min; (c)  $\text{PDC/4 \AA mol sieves/Et}_2\text{O/room temp.}$  1 h (54%); (xiv) (a)  $\text{MeLi/Et}_2\text{O}/-78^\circ\text{C}$  30 min; (b)  $\text{POCl}_3/\text{pyridine}$  (34%)

surface of the angular triquinane. However, for the silphiperfolene skeleton, the angular C-2- $\text{CH}_3$  would have already been installed in **5b**, and the aldehyde group of **8b** would need to be processed to enable connection to C-5.

For the silphinene skeleton, ketone **7a**<sup>7</sup> was the starting point. In view of the upcoming internal alkylation to connect C-6 and C-12 (see *a* in **8**, Scheme 1), we tried to preserve the C-11 carbonyl group; however, its presence proved to be problematic during attempts to cleave the benzylidene ring. The preferred strategy, therefore, was to carry out the Hanessian-Hullar<sup>8</sup> reaction on the protected alcohol **7b**, followed by reductive elimination<sup>9</sup> of the derived iodide **9** (Scheme 2) in order to obtain the alkenic aldehyde **10a** with *ca.* 3% of the C-2 epimer. Actually formation of the C-2 epimer was found to occur readily, as we discovered during attempts at deoxygenation. Thus, this task was best accomplished by treating the iodide **10b** with sodium borohydride in DMF,<sup>10</sup> which afforded the desired methyl group in **10c**. Transformation to the keto-iodide **11b** set the stage for the intramolecular alkylation which gave the C-12 epimers of **12** in a ratio of 1.5:1.<sup>†</sup> However, treatment with lithium bis(trimethylsilyl)amide, followed by exhaustive methylation gave **13**, and the alkene **14** was then prepared. Comparison of the latter with the racemic form of **14**, kindly supplied by Franck-Neumann,<sup>3g</sup> confirmed the validity of the route in Scheme 2 to the silphinene skeleton.

For silphiperfolene, the starting pyranosidodiquinane **7c** is more complex than **7a** (see Scheme 1) because of the presence of the C-10- $\text{CH}_3$  and C-2- $\text{CH}_3$ . The fact that the latter would have to be installed earlier than shown in **5b** meant that the C-3 carbonyl would be adjacent to a neopentenyl centre, and would, therefore, present a greater challenge to the reactions required to give **6b**.

Indeed, the resistance of **5b** toward any type of alkenation reaction<sup>2</sup> caused us to resort to the series of transformations **5b**  $\rightarrow$  **15** (Scheme 3) in order to obtain the primary allylic alcohol **16a**. Oxidation to the aldehyde, followed by addition of methylmagnesium chloride afforded the secondary allylic alcohol **16c**, which underwent the Claisen rearrangement<sup>2b</sup> stereoselectively to give aldehyde **6b**.

The standard radical cyclization of the idonitrile<sup>2</sup> related to **6b** gave the C-10 epimer of **7c**. In spite of the fact that the C-10- $\text{CH}_3$  was on the concave surface of the diquinane moiety, base catalysed epimerization was only partially successful. For this reason the spirocyclopentenone **17a** was prepared from **6b**, and conjugate radical addition now led to the desired C-10 epimer **7c** exclusively.

Deoxygenation at C-11 was best achieved by hydrogenation<sup>11</sup> of the corresponding enol triflate.<sup>12</sup>

With all transformations on the diquinane moiety now complete, the pyranoside ring was cleaved as described above leading to the alkenic aldehyde **18a**, an ideal intermediate for final conversion into silphiperfolene. Thus, the radical<sup>13,14</sup> obtained from **18b** underwent smooth 5-*exo* cyclization, and the product was processed to ketone **19** and thence to compound **2**.<sup>15</sup> Our sample of **2** had identical <sup>1</sup>H NMR spectra to the synthetic materials prepared by Meyers<sup>4d</sup> and Paquette.<sup>4a</sup> Our optical rotation was  $-79^\circ$  in comparison to  $-74.06^\circ$ ,<sup>4d</sup> and  $-34.2^\circ$ .<sup>4a</sup>

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<sup>†</sup> The unexpected formation of the *trans*-fused epimer of **12** as a substantial kinetic product may be due to the fact that the (presumed) transition state leading to the *cis*-epimer brings the C-5-OMOM and C-2- $\text{CH}_3$  into severe interaction.

determination of compounds **16d** and 10-*epi* **7c**, Professor Franck-Neumann<sup>3g</sup> for spectra of **14**, and to Professors Paquette<sup>4a</sup> and Meyers<sup>4d</sup> for spectra of **2**.

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## References

- 1 For a recent review, see B. Fraser-Reid and R. Tsang, in *Strategies and Tactics in Organic Synthesis*, ed. T. Lindberg, Academic Press, San Diego, California, 1989, vol. 2, ch. 4.
  - 2 (a) J. K. Dickson, Jr., R. Tsang, J. M. Llera and B. Fraser-Reid, *J. Org. Chem.*, 1989, **54**, 5350; (b) H. Pak, J. K. Dickson, Jr. and B. Fraser-Reid, *J. Org. Chem.*, 1989, **54**, 5357; (c) J. M. Llera and B. Fraser-Reid, *J. Org. Chem.*, 1989, **54**, 5544.
  - 3 For previous syntheses see: (a) L. A. Paquette and A. Leone-Bay, *J. Am. Chem. Soc.*, 1983, **105**, 7352; (b) T. Tsunoda, M. Kodama and S. Ito, *Tetrahedron Lett.*, 1983, **24**, 83; (c) D. D. Sternbach, J. W. Hughes, D. F. Burdi and B. A. Banks, *J. Am. Chem. Soc.*, 1985, **107**, 2149; (d) P. A. Wender and R. J. Ternansky, *Tetrahedron Lett.*, 1985, **26**, 2625; (e) M. T. Crimmins and S. W. Mascarella, *J. Am. Chem. Soc.*, 1986, **108**, 3435; (f) Y. K. Rao and M. Nagarayan, *J. Org. Chem.*, 1989, **54**, 5678; (g) M. Franck-Neumann, M. Miesch and E. Lacroix, *Tetrahedron Lett.*, 1989, **30**, 3533; (h) Y. Shizuri, M. Ohkubo and S. Yamamura, *Tetrahedron Lett.*, 1989, **30**, 3797.
  - 4 For previous syntheses see: (a) L. A. Paquette, R. A. Roberts and G. J. Drtina, *J. Am. Chem. Soc.*, 1984, **106**, 6690; (b) P. A. Wender and S. K. Singh, *Tetrahedron Lett.*, 1985, **26**, 5987; (c) D. P. Curran and S.-C. Kuo, *Tetrahedron*, 1987, **43**, 5653; (d) A. I. Meyers and B. A. Lefker, *Tetrahedron*, 1987, **43**, 5663; (e) K. Kakiuchi, M. Ue, H. Tsukahara, T. Shimizu, T. Miyao, Y. Tobe, Y. Odaira, M. Yasuda and K. Shima, *J. Am. Chem. Soc.*, 1989, **111**, 3707.
  - 5 (a) A. Klemer and G. Rodemeyer, *Chem. Ber.*, 1974, **107**, 2612; (b) R. Tsang and B. Fraser-Reid, *J. Chem. Soc., Chem. Commun.*, 1984, 60; (c) Y. Chapleur, *J. Chem. Soc., Chem. Commun.*, 1983, 141; (d) S. Handa, R. Tsang, A. T. McPhail and B. Fraser-Reid, *J. Org. Chem.*, 1987, **52**, 3489; (e) Y. Chapleur, R. Longchampbon and H. Gillier, *J. Chem. Soc., Chem. Commun.*, 1988, 564.
  - 6 D. B. Tulshian, R. Tsang and B. Fraser-Reid, *J. Org. Chem.*, 1984, **49**, 2347; B. Fraser-Reid, D. B. Tulshian, R. Tsang, D. Lowe and V. G. S. Box, *Tetrahedron Lett.*, 1984, **25**, 4579.
  - 7 R. Tsang and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1986, **108**, 2116.
  - 8 S. Hanessian, *Methods Carbohydr. Chem.*, 1972, **6**, 183.
  - 9 B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 1990; B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 2400; B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1979, **62**, 2411; B. Bernet and A. Vasella, *Helv. Chim. Acta*, 1984, **67**, 1328.
  - 10 M. Vol'pin, M. Dvolaitzky and I. Levitin, *Bull. Soc. Chim. Fr.*, 1970, 1526.
  - 11 V. B. Jigajinni and R. H. Wightman, *Tetrahedron Lett.*, 1982, **23**, 117; except Pd-C instead of PtO<sub>2</sub> was used.
  - 12 J. E. McMurry and W. J. Scott, *Tetrahedron Lett.*, 1983, **24**, 979.
  - 13 D. H. R. Barton and S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1*, 1974, 1574.
  - 14 M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, 1981, **103**, 932.
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