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Supplementary Material Available: Melting points, spectroscopic (IR and <sup>1</sup>H NMR) data, and elemental analyses for phosphine boranes 1,3-8, and 10 (5 pages). Ordering information is given on any current masthead page.

## Diastereotopic Selectivity at Prochiral Carbon Centers: Functionalization of Differentiated Hydroxymethyl **Groups Provides Access to Either Stereoisomeric** Configuration

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Synthetic methods that create new stereocenters with a high level of control are central to organic synthesis. Procedures that provide access to either stereoisomeric configuration can give rise to added flexibility. Recently, we described a reaction that proceeded with diastereotopic selectivity at a prochiral carbon center on route to a synthesis of talaromycin  $B^1$  (Scheme I). Subsequently, a procedure was developed that resulted in the reversal of diastereotopic selectivity and provided the stereocontrol required for the synthesis of talaromycin A.<sup>2b</sup> Herein, we report on an alternative method for the generation of either stereoisomeric configuration at a prochiral carbon center. In Scheme I a generalized system is depicted that represents a compound equipped with diastereotopic hydroxymethyl groups. Reaction processes that engage one of these groups selectively and nondestructively can be parlayed into the desired objective through suitable functionalization procedures.<sup>3</sup> In this study we have employed the spiroketalization reaction to illustrate this strategy for stereocontrol. This method, in conjunction with other features of the spiroketalization reaction, has been applied to a synthesis of  $(\pm)$ -invictolide (1) the fire ant queen recognition pheromone of Selonopsis invicta<sup>4,5</sup> and to a nonracemic synthesis of the  $C_1-C_9$ fragment 18 of the calcium ionophore ionomycin.<sup>6,7</sup>

The acyclic spiroketal precursor 2 has been prepared as a complex mixture of diastereomers<sup>8</sup> by two consecutive alkylations of the dimethylhydrazone of 3-pentanone.<sup>9</sup> Treatment of 2 with 4 equiv of camphorsulfonic acid in 10:1 methylene chloridemethanol at room temperature for 24 h resulted in the thermo-

(1) (a) Schreiber, S. L.; Sommer, T. J. Tetrahedron Lett. **1983**, 24, 4781. (b) Kozikowski, A. P.; Scripko, J. C. J. Am. Chem. Soc. **1984**, 106, 353. (c) Kocienski, P.; Yeates, C. J. Chem. Soc., Chem. Commun. 1984, 151. (d) Kay, I. T.; Bartholomew, D. Tetrahedron Lett. 1984, 25, 2035

(2) (a) Smith, A. B.; Thompson, A. S. J. Org. Chem. 1984, 49, 1469. (b) Schreiber, S. L.; Sommer, T. J.; Satake, K. Tetrahedron Lett. 1985, 26, 17. (c) Midland, M. M.; Gabriel, J. J. Org. Chem. 1985, 50, 1143

(3) For the functionalization of enantiotopic hydroxymethyl groups, see: Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. J. Am. Chem. Soc. **1979**, 101, 261.

(4) Isolation and synthesis: (a) Rocca, J. R.; Tumlinson, J. H.; Lofgren, C. S.; Glancey, B. M. *Tetrahedron Lett.* **1983**, *24*, 1893. Synthesis: (b) Hoye, T. R.; Peck, D. R.; Swanson, T. A. J. Am. Chem. Soc. 1984, 106, 2738.

(5) For other spiroketal-based strategies for the synthesis of nonspiroketal products, see: (a) Ireland, R. E.; Daub, J. P. J. Org. Chem. **1983**, 48, 1303, 1312, and ref 13. (b) Deslongchamps, P. "Stereoelectronic Effects in Organic Chemistry"; Pergamon Press: New York, 1983; Vol. 1, Chapter 8. (c) Deslongchamps, P.; Sauve, G.; Schwartz, D. A.; Ruest, L. Can. J. Chem. **1984**,

62, 2929. Spirolactone: (d) see ref 4b and 13. (6) Toeplitz, B. K.; Cohen, A. I.; Funke, P. T.; Parker, W. L.; Gougoutas, J. Z. J. Am. Chem. Soc. 1979, 101, 3344.

(7) (a) Evans, D A. Aldrichimica Acta 1982, 15, 23. (b) Wuts, P. G. M.;
 D'Costa, R.; Butler, W. J. Org. Chem. 1984, 49, 2582.
 (8) In addition to E/Z hydrazone stereoisomers, the three stereocenters

in 2 were prepared without stereocontrol, e.g.,

(9) Corey, E. J.; Enders, D. Tetrahedron Lett. 1976, 3.

Scheme I



Scheme II<sup>a</sup>



<sup>a</sup> (a) 1.3 equiv of LDA, THF, 0 °C, 15 h, then Br(CH<sub>2</sub>)<sub>3</sub>OEE, -78 °C, 2 h, 95%; (b) 1.3 equiv of LDA, THF, 0 °C, 20 h, then 2,2-dimethyl-5-iodomethyl-1,3-dioxane, -78 °C, 2 h (2 exists as a complex mixture of diastereomers), 91%; (c) 4 equiv of CSA, CH<sub>2</sub>Cl<sub>2</sub>-methanol (10:1), room temperature, 24 h (6:1 mixture of diasteromers), 88%.

dynamically controlled formation of a mixture of two major spiroketals in a 6:1 ratio (88% yield). The major diastereomer 3a is equipped with three equatorial substituents, whereas the minor component 3b contains an axial hydroxymethyl substituent. A trace amount of a third component (ca. 1%) was shown to contain the same spiroketal skeleton with an equatorial hydroxymethyl group and two axial methyl substituents. We did not observe any spiroketal isomer derived from the syn-1,3-dimethyl stereoisomer of 2 throughout the course of the reaction. Spiroketalization of this diastereomer would result in a syn-pentane interaction and was expected to be disfavored.<sup>12</sup> Presumably, prior equilibration through enolization is required for spiroketalization to occur. Each component gave rise to the same thermodynamic ratio of spiroketals upon resubjection to the equilibrating reaction conditions. The 6:1 equilibrium ratio of equatorial and axial hydroxymethyl-substituted spiroketals represents a pseudo A value of ca. 1.1 for this group at the 3-position of the tetrahydropyran ring system (Scheme II).

Two independent processes are operating in the conversion of 2 into 3. Equilibration at the carbon bearing the hydroxymethyl

<sup>(12)</sup> Deslongchamps, P.; Rowan, D. D.; Pothier, N.; Sauvé, T.; Saunders, J. K. Can. J. Chem. 1981, 59, 1105.



97:3 (equilibrium value)

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<sup>(10)</sup> Lynn, D. G.; Phillips, N. J.; Hutton, W. C.; Shabonowitz, J.; Fennell, D. I.; Cole, R. J. J. Am. Chem. Soc. 1982, 104, 7319

<sup>(11)</sup> Evans, D. A.; Sacks, C. E.; Kelschick, W. A.; Taber, T. R. J. Am. Chem. Soc. 1979, 101, 6789.

Scheme III<sup>a</sup>



<sup>a</sup> (d) 1.3 equiv of p-TsCl, py, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 48 h, 95%; (e) 2 equiv of LiEt<sub>3</sub>BH, THF, room temperature 2 h, 93%; (f) 100 equiv of BF<sub>3</sub>·OEt<sub>2</sub> HSCH<sub>2</sub>CH<sub>2</sub>SH, -40 °C, 2 h,  $(4 \rightarrow 5, 94\%)$ ;  $6 \rightarrow 7, 91\%$ ; (g) 2 equiv of t-BuPh, SiCl, 4 equiv of imidazole, DMF, room temperature, 30 min, 92%; (h) 2.6 equiv of p-TsCl, py, CH<sub>2</sub>Cl<sub>2</sub>, room temperature, 48 h, 88%; (i) 4 equiv of LiEt<sub>3</sub>BH, THF, room temperature, 2 h, 90%; (j) 6 equiv of n-Bu<sub>4</sub>NF, THF, room temperature, 2 h, 91%.

group occurs by ring opening of the spiroketal and reclosure with the alternate hydroxymethyl group. Stereocontrol in this manner was suggested by Lynn's studies of the equilibration of talaromycin A and B.<sup>10</sup> The acid-catalyzed equilibration of carbon centers  $\alpha$  and  $\alpha'$  to the spiroketal carbon was employed by Evans and co-workers in their synthesis of calcimycin<sup>11</sup> and has been examined in detail by the Deslongchamps group.<sup>12</sup> The Deslongchamps study provided the expectation that near complete anti-1,3-dimethyl stereocontrol could be obtained, as was observed. In the Hove synthesis of invictolide, the anti-1,3-dimethyl stereochemistry was obtained by a related spirolactonization reaction.<sup>13</sup> In this work, it would appear that the direct equilibration  $\alpha$  and  $\alpha'$  to the spirolactone could not be achieved, although this problem could be corrected through a recycling maneuver. The advantage of the spiroketal system for problems of this type is associated with this equilibration through transiently formed enol ether intermediates.

Tosylation and reduction of 3a afforded the trimethylated spiroketal 4 that could be ring opened to the acyclic derivative 5 without complications arising from epimerization by employment of the conditions of Ireland and Daub.<sup>14</sup> For the synthesis of invictolide, the opposite stereochemistry must be obtained at the carbon bearing the hydroxymethyl group of spiroketal 3. This can be achieved by silvlation of the hydroxyl (to afford 6) prior to the despiroketalization reaction. Bistosylation of the resultant diol 7, reduction with lithium triethylborohydride, and desilylation afforded the alcohol 8, which contains the proper stereochemistry for the invictolide synthesis (Scheme III).

To complete the synthesis, the problem of stereoselective lactone construction was addressed. Corey-Schmidt oxidation,<sup>15</sup> esterification, and hydrolysis of the dithiolane afforded keto ester 9. Reduction of the ketone with sodium borohydride provided a near 1:1 mixture of separable (HPLC) carbinol diastereomers. At this stage we could not make an assignment of stereochemistry at the carbinol site and felt we had little hope for significantly improving upon the stereoselectivity of the reduction. However, the ability to separate these diastereomers provided a simple solution to both of these problems.

The less mobile diastereomer lactonized directly to provide invictolide 1 upon treatment with catalytic trifluoroacetic acid in benzene and is thus assigned the structure 10. The more mobile diastereomer 11 provided an isomer of invictolide upon similar treatment. However, mesylation and saponification of 11 with excess base produced an inverted hydroxyl carboxylate that lactonized to afford invictolide 1 upon acidification. In this manner, Scheme IV<sup>a</sup>



<sup>a</sup> (a) 4 equiv of PDC, DMF, room temperature, 20 h, then  $CH_2N_2$ ,  $Et_2O$ , 86%; (b)  $HgCl_2$ ,  $CaCO_3$ ,  $CH_3CN-H_2O$  (4:1), room temperature, 3 h, 88%; (c) 2 equiv of NaBH<sub>4</sub>, MeOH, room temperature, 5 min (10/11 = 1:1), 95%; (d) catalytic CF<sub>3</sub>CO<sub>2</sub>H, benzene, room temperature, 2 h, 96%; (e) 20 equiv of MsCl, py, Et<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub> (4:1), 0 °C, 10 h, 87%; (f) 100 equiv of NaOH, MeOH-H, O (2:1), room temperature, 10 min, then HCl, 1 h, 96%.

both reduction products 10 and 11 could be stereospecifically converted to invictolide.16

A simple modification of the spiroketalization protocol can be employed to control the absolute stereochemistry of the resultant products. A suitably placed substituent along the spiroketal precursor serves as a device for the promotion of remote internal asymmetric induction. This is illustrated in the context of a synthesis of the  $C_1-C_9$  fragment of ionomycin 18, wherein the absolute stereochemistry of each carbon bearing a methyl group can be controlled in a single operation.

The S alcohol  $12^{17}$  was converted to the alkylating agent 13 and alkylated with a lithiated hydrazone to afford the acyclic spiroketal precursor 14 as a mixture of diastereomers. The thermodynamically controlled spiroketalization of this material produced a 8:1:0.1 mixture of three spiroketals, in analogy to the cyclization of  $2 \rightarrow 3^{18}$  The major spiroketal 15 results from participation of the S alcohol in the ketalization so as to place the (benzyloxy)methyl substituent in an equatorial orientation. The large A value expected of an alkyl group at this position (note 1,3-relationship to the spiro-carbon) ensures a high degree of stereocontrol in the reaction. The 1,4- and 1,6-asymmetric induction proceeds via the Evans-Deslongchamps equilibration and the 1,8-asymmetric induction is obtained through the diastereotopic selectivity (8:1) in the ketalization. The structure of ionomycin dictates that, in this instance, the free hydroxymethyl group should be converted to the methyl substituent. Subsequent despiroketalization of the trimethylated spiroketal 16 produced the dithiolane 17, which could be converted to the ionomycin fragment 18, by employment of the indicated conditions (Scheme V).<sup>19</sup> In

<sup>(13)</sup> See: ref 5b. Hoye, T. R.; Peck, D. R.; Trumper, P. K. J. Am. Chem. Soc. 1981, 103, 5618.

 <sup>(14)</sup> Ireland, R. E.; Daub, J. P. Tetrahedron Lett. 1982, 23, 3471.
 (15) Corey, E. J.; Schmidt, G. Tetrahedron Lett. 1979, 399.

<sup>(16)</sup> Comparison spectra were kindly provided by Dr. J. H. Tumlinson.<sup>4a</sup>
(17) [α]<sup>22</sup><sub>D</sub> -7.68° (c 3.67, MeOH) [lit. [α]<sup>23</sup><sub>D</sub> -7.56° (c 3.65, MeOH)];
(a) Tokano, S.; Kasahara, C.; Ogasawara, K. Chem. Lett. 1983, 175. (b) Katsuki, T.; Lee, A.; Ma, P.; Martin, V.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. J. Org. Chem. 1982, 47, 1373.
(18) The axial hydroxymetric light of the bid conductive bid conductive bid conductive bid conductive bid conductive for the bid conductive bid conductiv

<sup>(18)</sup> The axial hydroxymethyl isomer (15% yield) and the bis(axial methyl) isomer (ca. 1% yield) of 15 could be separated at this stage (HPLC). However, to facilitate material throughput these compounds were carried through as a mixture on larger scale operations until after the despiroketalization, where the easily separated acyclic diols 17 were purified by flash chromatography.

<sup>(19)</sup> An alternative four-step procedure (Ra-Ni, EtOH; NaIO<sub>4</sub>, MeOH; EVE: PDC, DMF) resulted in the formation of 15-20% of methyl epimers at the desulfurization step.<sup>20</sup> The indicated conditions (scheme V) completely avoided this problem.

<sup>(20)</sup> Koreeda, M.; Brown, L. J. Org. Chem. 1983, 48, 2122.



<sup>a</sup> (a) 1 equiv of *p*-TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 20 h, 78%; (b) CH<sub>2</sub>=CHOEt, ppts, 100%; (c) NaI, acetone, 83%; (d) metalated DMH prepared as before, THF, -78 °C, 91%; (e) 4 equiv of CSA, 10:1 CH<sub>2</sub>Cl<sub>2</sub>-MeOH, 2 days, then CF<sub>3</sub>SO<sub>3</sub>H, CH<sub>2</sub>Cl<sub>2</sub>, MeOH, -60 °C, 2 h, 80%; (f) *p*-TsCl, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 95%; (g) LiBEt<sub>3</sub>H, THF, 10 h, 93%; (h) HSCH<sub>2</sub>CH<sub>2</sub>SH, BF<sub>3</sub>·OEt<sub>2</sub>, -40 °C, 24 h, 92%; (i) Ac<sub>2</sub>O, Et<sub>3</sub>N, DMAP, CH<sub>2</sub>Cl<sub>2</sub>, 95%; (j) CaCO<sub>3</sub>, HgCl<sub>2</sub>, 4:1 CH<sub>3</sub>CN-H<sub>2</sub>O, 90%; (k) NaBH<sub>4</sub>, MeOH, 95%; (l) MsCl, pyridine, 4:1 Et<sub>2</sub>O-CH<sub>2</sub>Cl<sub>2</sub>, 98%; (m) LAH, Et<sub>2</sub>O, 0 °C, 2 days, 95%; (n) Pd/C, H<sub>2</sub>, EtOAc, 100%; (o) NaIO<sub>4</sub>, 1:1 THF-H<sub>2</sub>O, 95%, (p) CH<sub>2</sub>=CHOEt, ppts, 100%; (q) PDC, DMF, 81%.

this manner the S alcohol serves its final role as a carboxyl surrogate and provides a means of selectively adjusting the oxidation level of the  $C_1$  terminus of the ionomycin fragment 18.

In summary, the spiroketalization reaction with diastereotopic hydroxymethyl groups provides access to products with complementary stereochemistry. Other reaction processes that proceed with diastereotopic selectivity at prochiral carbon centers have been developed and will be the subject of future reports.

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## Novel Synthesis of Metacyclophanes. Thermal- and DDQ-Induced Aromatization of Bridgehead Dienes

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We have recently reported a general synthesis of bridgehead dienes utilizing a type II intramolecular Diels-Alder cycloaddition (eq 1).<sup>1</sup> The resulting bridgehead dienes 2 are 1,5-bridged



1,4-cyclohexadienes. The distortion imposed by the bridge constrains the 1,4-cyclohexadiene fragment to a boat conformation. The inherent reactivity of the ring system affords an opportunity for novel reaction manifolds not available to less strained species and a potential synthetic entry into topologically interesting molecules. A particularly intriguing possibility, illustrated in eq 2, involves dehydrogenation of the bridgehead diene to a metacyclophane.<sup>2</sup> Realization of this aromatization reaction would



offer a new entry into this interesting class of molecules that would complement existing methods.<sup>3</sup> The present paper reports the successful synthesis of metacyclophanes by dehydrogenation of bridgehead dienes and X-ray structural data for a derivative prepared by this method, a [6]metacyclophane.

Evidence for thermal dehydrogenation of bridgehead dienes was obtained by a careful analysis of the products of thermolysis (xylene, 260 °C, 2.8 h) from the intramolecular Diels-Alder cycloaddition of dienyne ether 4.<sup>4</sup> A GC mass spectrum of the thermolysate indicated that in addition to cycloadduct 5 (m/e 178), a smaller quantity of an aromatic side product (m/e 176) was also produced. In a subsequent investigation, it was learned that



thermolysis of bridgehead diene 5 (sealed tube, benzene, 259.5 °C) resulted in smooth dehydrogenation to metacyclophane 6 in quantative yield  $(t_{1/2} = 10 \text{ h})$ .

In addition to thermal dehydrogenation, bridgehead dienes may also be aromatized by treatment with DDQ. Thus, bridgehead diene 5 and 1.1 equiv of DDQ in toluene (25 °C, 6 h) affords the [7]metacyclophane 6 in 81% isolated yield. Since the bridgehead precursors are prepared by Diels-Alder chemistry, additional functionality is readily incorporated on the ring. For example, bridgehead diene ester 7, prepared by cycloaddition of the cor-



responding acyclic dienyne ester, was converted to [7]metacyclophane **8** in 64% isolated yield upon treatment with DDQ in toluene at reflux for 1 h. The methyl ester derivatives of these metacyclophanes have proven to be extremely valuable since they are crystalline compounds suitable for X-ray analysis.<sup>5</sup>

Extension of this methodology to the preparation of [6]metacyclophanes has also been accomplished. For example, the [6]metacyclophane **10** is isolated in 28% yield upon treatment of diene



<sup>(3)</sup> The chemistry of [n]metacyclophanes has been reviewed: Greenberg, A.; Liebman, J. F. "Strained Organic Molecules"; Academic Press: New York, 1978. More recent synthetic entries into [n]metacyclophanes can be found in: (a) Hirano, S.; Hara, H.; Hiyama, T.; Fujita, S.; Nozaki, H. *Tetrahedron* 1975, 31, 2219. (b) Turkenburg, L. A. M.; Blok, P. M. L.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* 1981, 3317. (c) Turkenburg, L. A. M.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* 1983, 1817. (d) Turkenburg, L. A. M.; van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. J. Am. Chem. Soc. 1980, 102, 3256.

<sup>(1)</sup> Shea, K. J.; Burke, L. D. J. Org. Chem. 1985, 50, 725. (b) Shea, K. J.; Burke, L. D., manuscript in preparation.

<sup>(2)</sup> An aromatization pathway to small [n]paracyclophanes has recently been reported by Gassman and co-workers: Gassman, P. G.; Bailey, T. F.; Hoye, R. C. J. Org. Chem. 1980, 45, 2923.

<sup>(4)</sup> All new compounds gave spectroscopic properties consistent with the assigned structures. The spectroscopic data for the metacyclophanes is included as supplemental information.

<sup>(5)</sup> The X-ray crystal structure for the [7]metacyclophane 8 will be published in the full acount of this work.