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A Global and Local Desymmetrization Approach to the Synthesis of Steroidal Alkaloids: Stereocontrolled Total Synthesis of Paspaline

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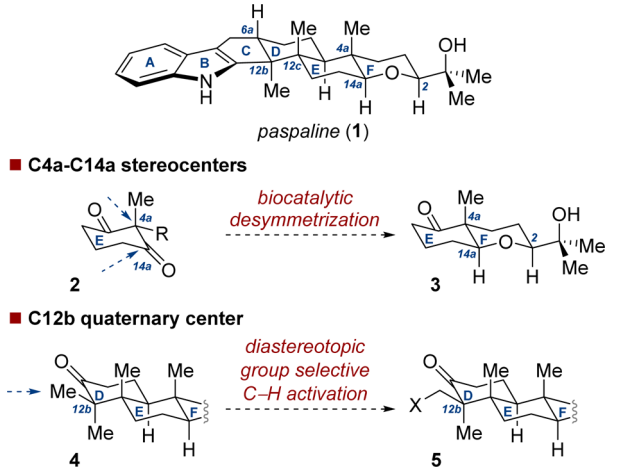
Supporting Information

ABSTRACT: A stereocontrolled total synthesis of the indole diterpenoid natural product paspaline is described. Key steps include a highly diastereoselective enzymatic desymmetrization, substrate-directed epoxidation, Ireland-Claisen rearrangement, and diastereotopic group selective C−H acetoxylation to assemble the target with excellent stereofidelity. The route and results described herein outline complementary conceptual disconnections in the arena of steroid natural product synthesis.

The terpene alkaloids represent a novel subset of natural products due to their unique biological profiles and their departure from the archetypal steroidal motif. The veratrums, for example, have been implicated in prostate, pancreatic, and breast cancers and, as a result, have been investigated as therapeutics.[1] Among these, jervine and cyclopamine have demonstrated marked inhibition of the hedgehog signaling pathway *in vitro* and are currently under study in clinical trials. The structurally distinct indole diterpenoids were first discovered from *Claviceps paspali* in the 1960s with the isolation of paspaline (**1**, Scheme 1);[2] related compounds including paspalinine,[3] paspalicine,[2] paxilline,[4] JBIR-03,[5] and others have since been reported.[6] Derivatives of paspalinine have shown potent activity as potassium channel antagonists and may be useful in the treatment of glaucoma.[7] JBIR-03 exhibits anti-MRSA activity and antifungal activity against apple Valsa canker-causing fungus, *Valsa ceratosperma*.[5]

Scheme 1. Synthesis Plan for Paspaline



As part of our ongoing efforts in applying stereoselective desymmetrization methods in the synthesis of chiral small molecules,[8,9] we identified paspaline and its related structures as exemplary targets for investigation. Paspaline's core structure presents a number of synthetic challenges, most notably its three all-carbon quaternary centers (C4a, C12b, C12c). Additionally, the 2,6-*cis*-tetrahydropyranyl F-ring is a unique departure from the classical steroid structure and requires careful synthetic planning for stereoselective assembly. These synthetic problems have been addressed through varied approaches since paspaline's discovery, significantly via the work of Smith of co-workers.[10] A number of total and partial synthetic studies of paspaline and related molecules have since been disclosed.[11] In developing our synthesis plan for paspaline, we noted that the majority of these approaches rely on the use of the Wieland-Miescher ketone as the key intermediate for establishing the C4a stereocenter. While this compound represents a classical "single stereocenter" desymmetrization,[12] we envisaged that a functionalized diketone such as **2** might set the stage for a more complex desymmetrization, simultaneously establishing both the C4a and C14a stereocenters via a biocatalytic diketone monoreduction (**3**) and introducing the functionality required for pyran assembly. In anticipation of the challenges associated with the late-stage creation of the C12b quaternary center,[10a] we hypothesized that a diastereotopic-group selective C−H activation on dimethyl ketone **4** or its derivatives would establish this critical stereocenter (**5**). This global and local desymmetrization approach would allow maximum control of stereochemical environments en route to **1**.

Our synthesis commenced with establishing the key C4a−C14a stereochemical relationship via reductive desymmetrization of diketone **6** (Scheme 2).[13] In a racemic sense, the reaction of this compound with $NaBH_4$ resulted in highly stereoselective monoreduction (20:1 dr), giving the opposite diastereomer to that required. Fortunately, biocatalytic monoreduction of **6** promoted by *Saccharomyces cerevisiae* completely overrode the inherent substrate bias, providing the desired (4a*R*,14a*S*)-relationship in **7** (paspaline numbering) with excellent diastereo- and enantioselectivity.[14,15] The remaining ketone was then converted to its tosyl hydrazone **8** in 97% yield. The reaction of trisubstituted alkene **8** with *m*-CPBA followed by PPTS led to a stereoselective epoxidation/intramolecular etherification sequence, providing the *cis*-pyran **9** directly in 77% yield and >20:1 dr (15 g scale), and thence

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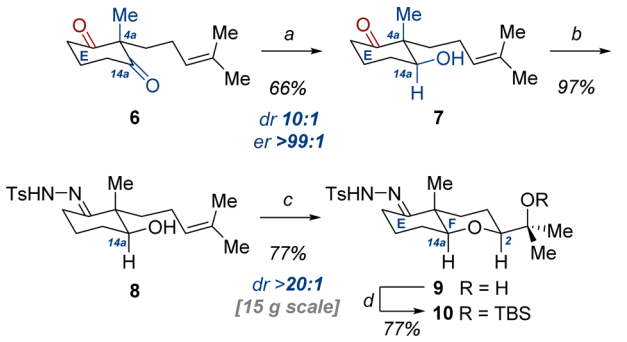
Scheme 2. Stereocontrolled Synthesis of E- and F-Rings[a]

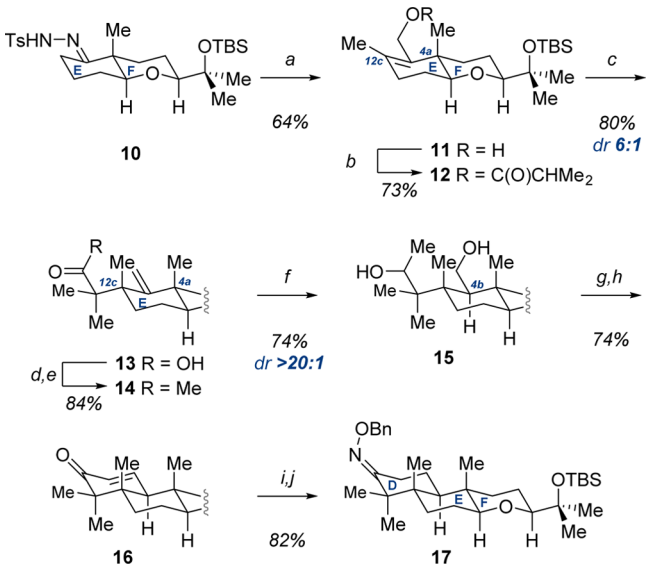


[a]Conditions: (a) YSC-2, H_2O:DMSO (10:1), 30 °C; (b) $TsHNNH_2$, C_7H_8, 70 °C; (c) *m*-CPBA, CH_2Cl_2, 0 °C, then PPTS (10 mol %), rt; (d) TBSOTf, 2,6-lutidine, CH_2Cl_2, −50 °C.

the silyl ether **10** upon treatment with TBSOTf. The hydrazone was compulsory for the success of the sequence; when the same epoxidation was carried out on the hydroxy ketone **7**, we isolated only the uncyclized oxirane with poor diastereoselectivity (<2:1). At this juncture, we speculate that the hydrazone in **8** plays a critical role in imposing a favorable reactive conformation on the cyclohexanol, placing the C14a hydroxyl in close proximity to the alkene during oxidation and subsequent ring closure. This reaction represents a rare case of a substrate-directed epoxidation in which the directing group is five carbons from the reaction center.[16]

Our next challenge was construction of the sterically congested D-ring in **1** (Scheme 3). We presumed that hydrazone **10** would provide a great deal of flexibility in

Scheme 3. D-Ring Construction and 1,3-Bis Angular Methyl Group Installation[a]

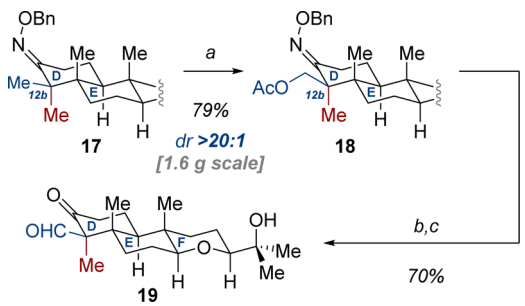


[a]Conditions: (a) *n*BuLi, THF, −50 °C, then MeI; *n*BuLi, −50 °C to rt, then $(HCHO)_n$; (b) isobutyric acid, DCC, DMAP (10 mol %), CH_2Cl_2, rt; (c) LDA, THF, −78 °C, then TMSCl, −78 to 75 °C; (d) $TMSCHN_2$, MeOH:C_7H_8 (2:1), rt; (e) MeLi, Et_2O, 0 °C to rt; (f) BH_3·THF, THF, 50 °C, then H_2O_2, NaOH, 0 °C to rt; (g) $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then DIPEA, −78 to 0 °C; (h) KOH, THF:MeOH (1:1), 0 °C to rt; (i) H_2 (1 atm), Pd/C (1.5 mass equiv), EtOAc, rt; (j) NH_2OBn·HCl, NaOAc, MeOH:H_2O (5:1), 85 °C.

investigating multiple approaches to D-ring assembly.[17] In the iteration that ultimately proved successful, α-methylation of the dianion derived from **10** followed by in situ deprotonation, Shapiro reaction, and trapping with $(HCHO)_n$ delivered the desired primary allylic alcohol **11** in 64% yield, which upon esterification, gave the isobutyrate **12**. To assemble the C12c angular methyl stereocenter, we surmised that the stereochemical outcome of an Ireland-Claisen reaction of ester **12** would be strongly influenced by the axial C4a methyl group; α-approach of the intermediate silyl ketene acetal would provide the requisite 1,3-*syn*-diaxial group relationship.[18] Indeed, enolization of **12** followed by silylation, heating, and hydrolysis gave the rearrangement product **13** in 80% yield and 6:1 dr. This reaction was the only step in the synthesis that proceeded with less than complete stereocontrol. Esterification and nucleophilic methylation provided the ketone **14** in 84% yield over two steps. Hydroboration/oxidation of **14** proceeded with virtually complete selectivity at C4b to afford diol **15** in 74% yield, and subsequent global oxidation and cyclocondensation concluded D-ring assembly (**16**). Hydrogenation of **16** and condensation of the ketone with *O*-benzyl hydroxylamine proceeded smoothly, giving oxime **17** in 82% yield.

Focus then turned to local desymmetrization to create the C12b all-carbon quaternary stereogenic center (Scheme 4).

Scheme 4. Local Desymmetrizing C−H Activation to Establish C12b Angular Methyl Stereochemistry[a]



[a]Conditions: (a) $Pd(OAc)_2$ (15 mol %), $PhI(OAc)_2$, $AcOH:Ac_2O$ (1:1), 100 °C; (b) HCl, H_2O:MeOH:THF:acetone (10:10:10:1), 85 °C; (c) DMP, CH_2Cl_2, rt.

Cognizant of the fact that the lowest-energy conformation of **17** places the C−N π-bond in plane with the equatorial methyl group, we implemented a directed C−H activation reaction inspired by the report of Sanford and co-workers.[19,20] In the event, the direct application of Sanford's conditions to oxime **17** provided the desired monoacetate **18** in 79% yield as a single diastereomer (1.6 g scale). This transformation completed assembly of the final quaternary center, which upon global deprotection and oxidation, gave ketoaldehyde **19** poised for synthesis completion.

From tricycle **19**, there remained the challenges of establishing the C6a methine stereocenter and C-ring construction (Scheme 5). The needed carbon atoms were incorporated by bis-vinylation of **19** to give diol **20**,[21] which, upon ring-closing metathesis, provided allylic alcohol **21** in 71% yield. Acid-catalyzed elimination cleanly delivered the unconjugated enone **22**, which participated in a highly stereoselective catalytic hydrogenation (Pd/C), providing exclusively the epimeric C6a methine stereocenter. This selectivity was not altogether unexpected; catalytic hydrogenation of related steroidal systems have been documented to proceed from the

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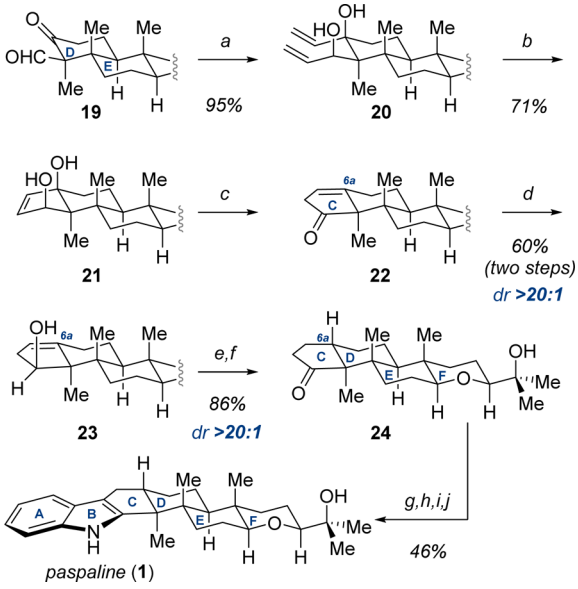
Scheme 5. C-Ring Construction and Synthesis Completion[a]



[a]Conditions: (a) vinylmagnesium bromide, $CeCl_3$·2LiCl, THF, −78 °C; (b) Grubbs second gen. catalyst (20 mol %), CH_2Cl_2, rt; (c) TFA, CH_2Cl_2, 0 °C to rt; (d) $LiAlH_4$, THF, 0 °C; (e) H_2 (1 atm), $[C_8H_{12}]IrP(C_6H_{11})_3C_5H_5N]PF_6$ (15 mol %), CH_2Cl_2, rt; (f) DMP, CH_2Cl_2, rt. (g) LDA, THF, 0 °C, then HMPA, Me_2S_2; (h) *N*-chloroaniline, CH_2Cl_2, −78 °C, then NEt_3; (i) Raney Ni, EtOH, rt; (j) TsOH (66 mol %), CH_2Cl_2, 50 °C.

convex face of the bicycle.[22] To circumvent this issue, we envisaged reduction of the ketone in **22** might also proceed with analogous convex-face selectivity to give the corresponding alcohol, which would serve as a substrate for directed alkene reduction.[23] Indeed, reduction of **22** upon treatment with $LiAlH_4$ gave exclusively the (*S*)-hydroxyl **23** in 60% yield over two steps. The stereochemistry of this reaction is of note in that reduction of analogous compounds not bearing the C12a angular methyl group in **1** have proceeded with selectivity orthogonal to that observed in **23**,[22,24] giving evidence to the impact of this methyl group in facial preference of the ketone in **22**. Catalytic hydrogenation of **23** using Crabtree's catalyst and subsequent oxidation gave ketone **24** in 86% yield over two steps with complete concave surface selectivity. To complete our synthesis, the Gassman indolization of **24** previously employed by Smith proved effective in affording paspaline (**1**) in 46% yield over four steps.[10a,25] In addition to matching the reported analytical data,[2a,10d] an X-ray diffraction study of synthetic paspaline provided secondary confirmation of the final structure[3c] and the sense of enantioinduction imposed in the biocatalytic desymmetrization.[26]

In summary, a global and local symmetry-breaking approach to the total synthesis of the indole diterpenoid paspaline is reported. Central to our strategy was the implementation of a biocatalytic monoreduction and directed epoxidation to create the E-F bicycle, and a diastereotopic group selective C−H acetoxylation to assemble the C12b quaternary center. The synthesis collectively demonstrates the viability of these methods in the arena of steroid total synthesis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization, and spectral data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Heretsch, P.; Tzagkaroulaki, L.; Giannis, A. *Angew. Chem., Int. Ed.* **2010**, *49*, 3418.

(2) (a) Fehr, T.; Acklin, W. *Helv. Chem. Acta* **1966**, *49*, 1907. (b) Gysi, R. P. Ph.D. Dissertation No. 4990, Eidgenossiche Technische Hochschule, Zürich, Switzerland, 1973. (c) Leutwiler, A. Dissertation No. 5163, Eidgenossiche Technische Hochschule, Zürich, Switzerland, 1973. (d) Springer, J. P.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 231 and references therein.

(3) (a) Cole, R. J.; Dorner, J. W.; Lansden, J. A.; Cox, R. H.; Pape, C.; Cunfer, B.; Nicholson, S. S.; Bedell, D. M. *J. Agric. Food Chem.* **1977**, *25*, 1197. (b) Cole, R. J.; Dorner, J. W.; Springer, J. P.; Cox, R. H. . *Agric. Food Chem.*. **1981**, *29*, 293. (c) Gallagher, R. T.; Finer, J.; Clardy, J.; Leutwiler, A.; Weibel, F.; Acklin, W.; Arigoni, D. *Tetrahedron Lett.* **1980**, *21*, 235.

(4) (a) Cole, R. J.; Kirksey, J. W.; Wells, J. M. *Can. J. Microbiol.* **1974**, *20*, 1159. (b) Springer, J. P.; Clardy, J.; Wells, J. M.; Cole, R. J.; Kirksey, J. W. *Tetrahedron Lett.* **1975**, *16*, 2531.

(5) Ogata, M.; Ueda, J.-y.; Hoshi, M.; Hashimoto, J.; Nakashima, T.; Anzai, K.; Takagi, M.; Shin-ya, K. *J. Antibiot.* **2007**, *60*, 645.

(6) (a) Wilson, B. J.; Wilson, C. H. *Science (Washington, D.C.)* **1964**, *144*, 177. (b) Gallagher, R. T.; Clardy, J.; Wilson, B. J. *Tetrahedron Lett.* **1980**, *21*, 239. (c) De Jesus, A. E.; Steyn, P. S.; Van Heerden, F. R.; Vleggaar, R.; Wessels, P. L.; Hull, W. E. *J. Chem. Soc., Chem. Commun.* **1981**, 289. (d) Wilson, B. J.; Wilson, C. H.; Hayes, A. W. *Nature (London, U.K.)* **1968**, *220*, 77.

(7) (a) Brnardic, E.; Doherty, J. B.; Dorsey, J.; Ellwood, C.; Fillmore, M.; Malaska, M.; Nelson, K.; Soukri, M. Preparation of Indole Diterpene Alkaloids as Maxi-K Channel Blockers for the Treatment of Glaucoma. WIPO 2009/048559, 2009. (b) Garcia, M. L.; Goetz, M. A.; Kaczorowski, G. J.; McManus, O. B.; Monaghan, R. L.; Strohl, W. R.; Tkacz, J. S. Novel Maxi-K Channel Blockers, Methods of Use and Process for Making the Same. U.S. Patent 0239863, 2005.

(8) (a) Malinowski, J. T.; Sharpe, R. J.; Johnson, J. S. *Science* **2013**, *340*, 180. (b) Sharpe, R. J.; Malinowski, J. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2013**, *135*, 17990. (c) Corbett, M. T.; Johnson, J. S. *Chem. Sci.* **2013**, *4*, 2828.

(9) For reviews and selected recent examples of the use of stereoselective desymmetrization in synthesis, see (a) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167. (b) Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765. (c) Inuoe, M.; Sato, T.; Hirama, M. *J. Am. Chem. Soc.* **2003**, *125*, 10772. (d) Karatholuvhu, M. S.; Sinclair, A.; Newton, A. F.; Alcaraz, M.-L.; Stockman, R. A.; Fuchs, P. L. *J. Am. Chem. Soc.* **2006**, *128*, 12656. (e) Qi, J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 12682. (f) Nicolaou, K. C.; Li, A.; Edmonds, D. J.; Tria, G. S.; Ellery, S. P. *J. Am. Chem. Soc.* **2009**, *131*, 16905. (g) Nagatomo, M.;

DOI: 10.1021/jacs.5b02631
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

Koshimizu, M.; Masuda, K.; Tabuchi, T.; Urabe, D.; Inoue, M. *J. Am. Chem. Soc.* **2014**, *136*, 5916. (h) Yang, M.; Li, J.; Li, A. *Nat. Commun.* **2015**, *6*, 6445.

(10) (a) Smith, A. B., III; Mewshaw, R. *J. Am. Chem. Soc.* **1985**, *107*, 1769. (b) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2787. (c) Smith, A. B., III; Leenay, T. L. *Tetrahedron Lett.* **1988**, *29*, 2791. (d) Mewshaw, R. E.; Taylor, M. D.; Smith, A. B., III. *J. Org. Chem.* **1989**, *54*, 3449. (e) Smith, A. B., III; Leenay, T. L. *J. Am. Chem. Soc.* **1989**, *111*, 5761. (f) Smith, A. B., III; Sunazuka, T.; Leenay, T. L.; Kingery-Wood, J. *J. Am. Chem. Soc.* **1990**, *112*, 8197. (g) Smith, A. B., III; Kingery-Wood, J.; Leenay, T. L.; Nolen, E. G.; Sunazuka, T. *J. Am. Chem. Soc.* **1992**, *114*, 1438. (h) Smith, A. B., III; Ohta, M.; Clark, W. M.; Leahy, J. W. *Tetrahedron Lett.* **1993**, *34*, 3033. (i) Smith, A. B., III; Nolen, E. G.; Shirai, R.; Blase, F. R.; Ohta, M.; Chida, N.; Hartz, R. A.; Fitch, D. M.; Clark, W. M.; Sprengeler, P. A. *J. Org. Chem.* **1995**, *60*, 7837. (j) Smith, A. B., III; Hartz, R. A.; Spoors, P. G.; Rainier, J. D. *Israel J. Chem.* **1997**, *37*, 69. (k) Smith, A. B., III; Kanoh, N.; Minakawa, N.; Rainier, J. D.; Blase, F. R.; Hartz, R. A. *Org. Lett.* **1999**, *1*, 1263. (l) Smith, A. B., III; Kanoh, N.; Ishiyama, H.; Hartz, R. A. *J. Am. Chem. Soc.* **2000**, *122*, 11254. (m) Smith, A. B., III; Davulcu, A. H.; Kürti, L. *Org. Lett.* **2006**, *8*, 1665. (n) Smith, A. B., III; Kürti, L.; Davulcu, A. H.; Cho, Y. S.; Ishiyama, H.; Ohmoto, K. *J. Org. Chem.* **2007**, *72*, 4611.

(11) (a) Guile, S. D.; Saxton, J. E.; Thornton-Pett, M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1763. (b) Clark, J. S.; Myatt, J.; Roberts, L.; Walshe, N. *Synlett* **2005**, 697. (c) Churruca, F.; Fousteris, M.; Ishikawa, Y.; Rekowski, M. W.; Hounsou, C.; Surrey, T.; Giannis, A. *Org. Lett.* **2010**, *12*, 2096. (d) Enomoto, M.; Kuwahara, S. *J. Org. Chem.* **2010**, *75*, 6286. (e) Bradshaw, B.; Etxebarria-Jardi, G.; Bonjoch, J. *J. Am. Chem. Soc.* **2010**, *132*, 5966. (f) Oikawa, M.; Hashimoto, R.; Sasaki, M. *Eur. J. Org. Chem.* **2011**, 538. (g) Isaka, T.; Hasegawa, M.; Toshima, H. *Biosci. Biotechnol. Biochem.* **2011**, *75*, 2213. (h) Adachi, M.; Higuchi, K.; Thasasa, N.; Yamada, H.; Nishikawa, T. *Org. Lett.* **2012**, *14*, 114. (i) Okano, K.; Yoshii, Y.; Tokuyama, H. *Heterocycles* **2012**, *84*, 1325. (j) Enomoto, M.; Morita, A.; Kuwahara, S. *Angew. Chem., Int. Ed.* **2012**, *51*, 12833. (k) Bian, M.; Wang, Z.; Xiong, X.; Sun, Y.; Matera, C.; Nicolaou, K. C.; Li, A. *J. Am. Chem. Soc.* **2012**, *134*, 8078. (l) Goetz, A. E.; Silberstein, A. L.; Corsello, M. A.; Garg, N. K. *J. Am. Chem. Soc.* **2014**, *136*, 3036.

(12) (a) Eder, U.; Sauer, G.; Wiechert, R. *Angew. Chem.* **1971**, *83*, 492. (b) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1973**, *38*, 3239. (c) Hajos, Z. G.; Parrish, D. R. *J. Org. Chem.* **1974**, *39*, 1615. (d) Micheli, R. A.; Hajos, Z. G.; Cohen, N.; Parrish, D. R.; Portland, L. A.; Sciamanna, W.; Scott, M. A.; Wehrli, P. A. *J. Org. Chem.* **1975**, *40*, 675.

(13) Ketone **6** was synthesized via a modification of Enders' procedure. Demir, A. S.; Enders, D. *J. Prakt. Chem.* **1997**, *339*, 553.

(14) (a) Watanabe, H.; Iwamoto, M.; Nakada, M. *J. Org. Chem.* **2005**, *70*, 4652. (b) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Nakashima, Y.; Kajimoto, T.; Node, M. *Synlett* **2006**, 2176. (c) Katoh, T.; Mizumoto, S.; Fudesaka, M.; Takeo, M.; Kajimoto, T.; Node, M. *Tetrahedron: Asymmetry* **2006**, *17*, 1655.

(15) For examples of this type of transformation in total synthesis, see: (a) Yeung, Y.; Chein, R.-J.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 10346. (b) Liu, L. L.; Chiu, P. *Chem. Commun.* **2011**, *47*, 3416. (c) Breitler, S.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2013**, *52*, 11168.

(16) Other examples of remote direction in alkene functionalization: (a) Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286. (b) Wan, K. K.; Iwasaki, K.; Umotoy, J. C.; Wolan, D. W.; Shenvi, R. A. *Angew. Chem., Int. Ed.* **2015**, *54*, 2410.

(17) (a) Shapiro, R. H.; Heath, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 5734. (b) Shapiro, R. H. *Org. React. (N.Y., Engl. Transl.)* **1975**, *23*, 405.

(18) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(19) (a) Desai, L. V.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 9542. (b) Neufeldt, S. R.; Sanford, M. S. *Org. Lett.* **2010**, *12*, 532.

(20) (a) Siler, D. A.; Mighion, J. D.; Sorenson, E. J. *Angew. Chem., Int. Ed.* **2014**, *53*, 5332. (b) Meng, Z.; Yu, H.; Li, L.; Tao, W.; Chen, H.; Wan, M.; Yang, P.; Edmonds, D.; Zhong, J.; Li, Ang. *Nat. Commun.* **2015**, *6*, 6096.

(21) Krasovskiy, A.; Kopp, F.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 497.

(22) Abad, A.; Agullo, C.; Arno, M.; Domingo, L. R.; Zaragoza, R. J. *J. Org. Chem.* **1990**, *55*, 2369 and references therein.

(23) (a) Evans, D. A.; Morrissey, M. *J. Am. Chem. Soc.* **1984**, *106*, 3866. (b) Evans, D. A.; Morrissey, M. *Tetrahedron Lett.* **1984**, *25*, 4637.

(24) (a) St. André, A. F.; MacPhillamy, H. B.; Nelson, J. A.; Shabica, A. C.; Scholz, C. R. *J. Am. Chem. Soc.* **1952**, *74*, 5506. (b) Gabbard, R. B.; Segaloff, A. *Steroids* **1983**, *41*, 791. (c) Haddad, M.; Blazejewski, J. C.; Wakselman, C.; Dorai, V.; Duc, I. *Eur. J. Med. Chem.* **1994**, *29*, 627. (d) Khripach, V. A.; Zhabinskii, V. N.; Fando, G. P.; Kuchto, A. I.; Lyakhov, A. S.; Govorova, A. A.; Groen, M. B.; van der Louw, J.; De Groot, A. *Steroids* **2004**, *69*, 495.

(25) Gassman, P. G.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*, 5495.

(26) CCDC 1052642 contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Centre via www.ccdc.cam.ac.uk/data_request/cif.

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