dination of the primary alcohol and reductive elimination provided the β-ketoester 6 which exists as a ca. 1:1 mixture of ketone and hemiketal forms. Selective silylation of the primary alcohol effectively trapped this system as its open chain derivative, and subsequent chelation-controlled reduction provided the syn 3,5-diol 7 by a modified Narasaka methodology.[8] While at this point the relative disposition of the hydroxyl groups could not be unequivocally ascertained, the syn assignment was supported by 500-MHz ^{1}H NMR decoupling experiments on the corresponding acetonide 8 and was subsequently confirmed by X-ray crystallography.[9] Ozonolysis provided the aldehyde 1 which corresponds to the C_1–C_9 portion of 6-deoxyerythronolide B.

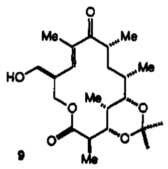
As shown, thermodynamically controlled spiroketalization provides an effective method for controlling the stereochemistry of multiple centers relative to an initial element of stereogenicity. Added flexibility comes from the possible use of the intermittent spiro system as a template for subsequent kinetically controlled transformations. While we chose here to synthesize the C_1–C_9 portion of 6-deoxyerythronolide B, application to a number of other systems may also be possible. Either axial or equatorial hydroxyl functions can be obtained by ketone reduction in the cyclic species, dependent upon the choice of reaction conditions. Further, in the acyclic chain, reduction of a β-ketone function allows access to either syn or anti 1,3-diols. Moreover, spiroketal ring opening by reductive elimination provides a terminal olefin that allows access to a variety of other functional groups.[10]

In summary, the thermodynamic spiroketalization reaction is an effective device for the preparation of distal stereogenic centers. In the example shown, two centers, controlled at an early stage of the sequence, are ultimately responsible for dictating the appropriate stereochemical relationships at five contiguous centers in an acyclic target.[11]

Acknowledgment. This work was supported by the National Institute of General Medical Sciences (GM-32527). We thank Gayle Schulte of the Yale University Instrument Center for determination of X-ray crystal structures.[12]

(8) (a) Narasaka, K.; Pai, F. *Tetrahedron* 1984, *40*, 2233–2238. (b) Sletzinger, M.; Verhoeven, T. R.; Volante, R. P.; McNamara, J. M.; Corley, E. G.; Liu, T. M. H. *Tetrahedron Lett.* 1985, *26*, 2951–2954.

(9) The stereochemistry of these centers (C_3 and C_5) was confirmed at a later stage in our synthetic studies by the preparation of lactone 9 as determined by X-ray crystallography. Coordinates are available in the supplementary material. Our studies in this area will be reported elsewhere.

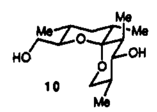


9

(10) Transketalization is also an option here. See: Schromburg, D.; Hopkins, P. B.; Lipscomb, W. N.; Corey, E. J. *J. Org. Chem.* 1980, *45*, 1544–1546. Ireland, R. E.; Daub, J. P. *Tetrahedron Lett.* 1982, *23*, 3471–3474.

(11) This work was taken from the Ph.D. thesis of N. I. Totah, Yale University, 1990.

(12) These structures are the equatorial alcohol 10, shown below, and lactone 9 (see ref 9). Coordinates are available in the supplementary material.



10

Direct Syntheses of Polyfused Ring Systems by Intramolecular Tandem Palladium–Ene/Heck Insertion Reactions

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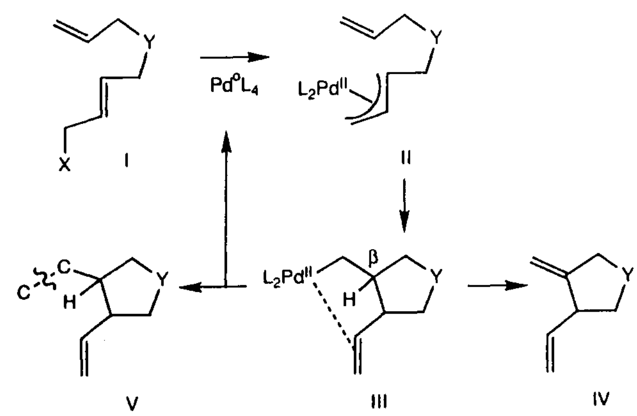
Summary: The Pd(0)-catalyzed polycyclizations **1** → **3** + **4**, **5** → **9** and **6** → **10** are described. The stereospecifity of these transformations is ascribed to an intramolecular suprafacial "palladium–ene" process followed by one to two "Heck-insertions" proceeding with retention of configuration at the metalated carbon.

Palladium- and nickel-catalyzed intramolecular allylations I → IV have been recently shown to provide a variety of carbo- and heterocycles in a stereospecific fashion.[1] The β-elimination step, e.g., III → IV, is relatively fast. Thus, trapping of the transient σ-alkylpalladium species with formation of a new carbon–carbon bond III → V was so far limited to carbonylation reactions.[1]

Scheme I

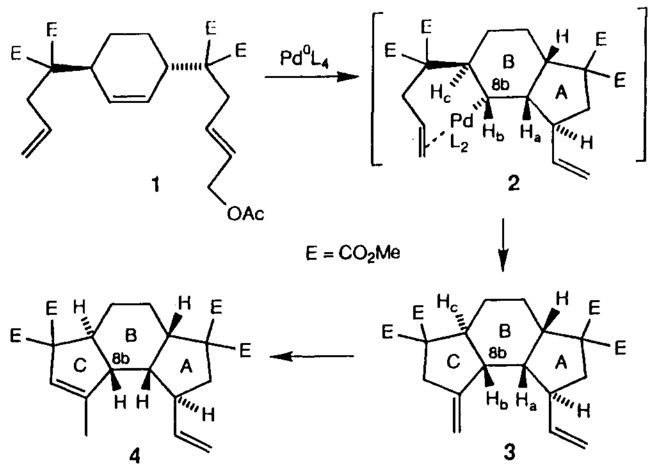


We report here intramolecular insertions of σ-palladium intermediates III into simple olefinic bonds (Heck inser-

(1) Oppolzer, W.; Gaudin, J.-M. *Helv. Chim. Acta* 1987, *70*, 1477. Reviews: Oppolzer, W. *Angew. Chem.* 1989, *101*, 39; *Angew. Chem., Int. Ed. Engl.* 1989, *28*, 38. Oppolzer, W. *Pure Appl. Chem.* 1990, *62*, 1941.

0022-3263/91/1956-6256$02.50/0

Scheme II

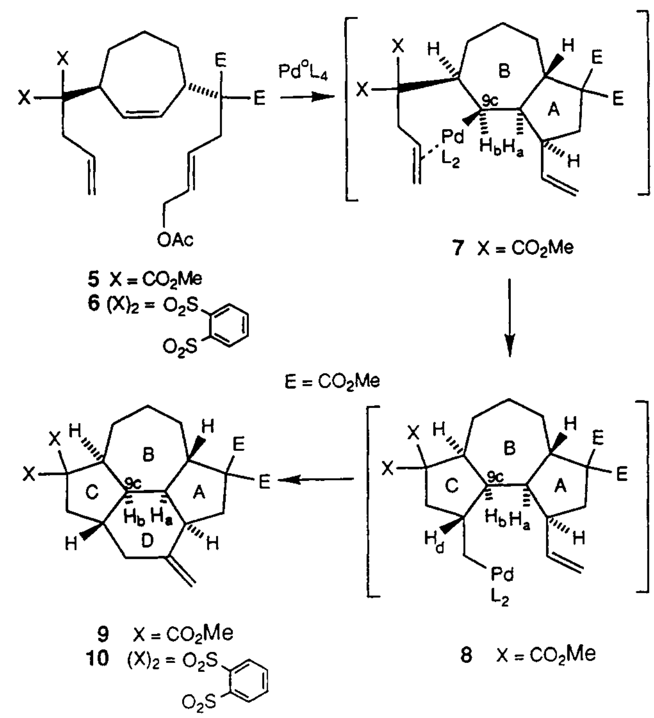


tions) which compete efficiently with the β-elimination process.[2]

Heating *trans*-trienyl acetate 1[3,7] with $Pd(dba)_2$ (dba = dibenzylideneacetone,[3] 0.1 mol equiv) and trifurylphosphine (0.5 mol equiv) in acetic acid at 110 °C for 1 h, followed by chromatography on $AgNO_3$-impregnated silica gel furnished crystalline *exo*-methylene *as*-indacene 3[7] (28%, mp 136 °C, from Et_2O) and the less polar olefinic isomer 4 (42% oil). The product ratio 4/3 of the crude reaction mixture increased from 60:40 to >94:<6 on treatment with *p*-toluenesulfonic acid in CH_2Cl_2 at rt (^{1}H NMR). It thus appears that under the cyclization conditions part of the initially formed *exo*-methylene product 3 isomerized to the more stable endocyclic olefin 4.

X-ray diffraction analysis of crystalline product 3[8] shows the central cyclohexane ring B being cis-fused to the ring A and trans-fused to the ring C. The angular hydrogen atoms H_a/H_b in product 3 are cis-disposed, consistent with a suprafacial carbometalation 1 → 2 and a subsequent C—Pd/C=C insertion 2 → 3 with retention of configuration at C(8b).[9] This implies that the intramolecular Heck reaction 2 → 3 predominates over β-elimination although σ-palladium intermediate 2 does possess a syn-β-hydrogen Hc.

Scheme III



An even more remarkable polycyclization was observed on heating the homologous 1,4-*trans*-cycloheptene substrate 5[3,7] with $Pd(dba)_2$ (0.1 mol equiv)/trifurylphosphine (0.4 mol equiv)/HOAc/110 °C/2 h. Chromatography ($AgNO_3$ impregnated SiO_2) afforded crystalline cyclohept[*jkl*]-*as*-indacene 9 in 50% yield. A recrystallized sample (hexane/EtOAc, mp 138–139 °C) was shown by X-ray diffraction evidence to possess structure 9.[8]

We thus conclude that tetracyclic product 9 has been formed via Pd-ene cyclization of 5 (closing ring A) followed by *two* intramolecular Heck reactions (closing rings C and D). Rings A and B in product 9 are trans fused (in contrast to product 3) which indicates a different topicity of the initial allylation step. Nevertheless, hydrogen atoms H_a/H_b in product 9 are again cis related in agreement with a suprafacial Pd-ene process and subsequent Heck insertion with retention of configuration at C(9c) giving σ-alkylpalladium intermediate 7. A Dreiding model of postulated tricyclic σ-Pd complex 8 exhibits a relatively rigid conformation enforcing proximity of the metal and the vinyl group. Hence the second C—Pd/C=C insertion 8 → 9 becomes favored over β-elimination of 8. Analogous Pd-catalyzed cyclization of disulfone 6[3,7] gave after crystallization a tetracyclic product[7] (ether, mp 297–299 °C dec, 66% yield) tentatively assigned configuration 10.

The scope and limitations of these results are being further explored in our laboratories.

Acknowledgment. Financial support of this work by the Swiss National Science Foundation, Sandoz Ltd., Basel, and Givaudan SA, Vernier, is gratefully acknowledged. We thank The National Science Foundation, USA, for a Postdoctoral Fellowship to R.J.D.

(2) Several laboratories have reported Pd-catalyzed polyene or enyne cyclizations via Heck insertions of Pd intermediates incapable of β-elimination: Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem.* **1989**, *54*, 5846–48. Abelman, M. M.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 2328–2329. Zhang, Y.; Negishi, E.-I. *J. Am. Chem. Soc.* **1989**, *111*, 3454–3456. Wu, G. Z.; Lamaty, F.; Negishi, E.-I. *J. Org. Chem.* **1989**, *54*, 2507–2508. Grigg, R.; Dorrity, M. J.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 1343. Trost, B. M.; Shi, Y. *J. Am. Chem. Soc.* **1991**, *113*, 701 and references cited therein. See also: Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557–3568. Larock, R. C.; Fried, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 5882–5884.

(3) $Pd(dba)_2$ prepared as described by: Rettig, M. F.; Maitlis, P. M. *Inorg. Synth.* **1977**, *17*, 134. Racemic, diastereomerically pure trienyl precursors were prepared as follows. 1: (i) Dimethyl allylmalonate,[4] NaH, DMF 0 °C → rt; addition of *cis*-1-acetoxy-4-chloro-2-cyclohexene,[5] 0 °C → rt, 16 h giving dimethyl (*trans*-4-acetoxy-2-cyclohexenyl)allylmalonate (85%); (ii) dimethyl malonate, NaH, DMSO, rt, 2 h; addition of $Pd(dba)_2$, PPh_3, then dimethyl (*trans*-4-acetoxy-2-cyclohexenyl)allylmalonate 120 °C, 3 h; (iii) resulting dimethyl [*trans*-4-[(dimethoxycarbonyl)methyl]-2-cyclohexenyl]allylmalonate, NaH, THF, rt, 1.5 h; addition of $Pd(dba)_2$, PPh_3; addition of *trans*-1-acetoxy-4-chloro-2-butene[6] at 0 °C then rt, 16 h giving 1 (71%). 5. As described for 1 but starting from *cis*-1-acetoxy-4-chloro-2-cycloheptene.[5] 6: 1,3-Benzodithiole tetraoxide,[6] NaH, DMF, 0 °C → rt; addition of *cis*-1-acetoxy-4-chloro-2-cycloheptene, rt 24 h; (ii) resulting 2-(*trans*-4-acetoxy-2-cycloheptenyl)-1,3-benzodithiol tetraoxide, NaH, DMF, 0 °C → rt; addition of allyl bromide 0 °C → rt; following steps in analogy to steps (ii) and (iii) as described for 1.

(4) Bäckvall, J. E.; Nyström, J. E.; Nordberg, R. E. *J. Am. Chem. Soc.* **1985**, *107*, 3676.

(5) Brillon, D. *Synth. Commun.* **1986**, *16*, 291.

(6) Kündig, E. P.; Cunningham, A. F. *Tetrahedron* **1988**, *44*, 6855.

(7) All new compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS.

(8) Bernardinelli, G.; Oppolzer, W.; DeVita, R. *Acta Crystallogr.*, in print.

(9) The stereospecific polymerization of propylene has been rationalized by postulating syn-additions of transition-metal alkyls to propylene: cf. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: 1987; p 587.