stereochemistry of the substituents in the precursor is retained in the cyclization.

Bifunctional silicon reagents offer an excellent opportunity to store chemical reactivity, which can be selectively unleashed. While a halosilane can be thought of as a zwitterion equivalent, the ability to selectively metalate the bromide or activate the allylsilane also permits such species to serve as dianion equivalents. As the results herein show, this dianion equivalence can serve as a valuable cyclization approach to both carbo- and heterocyclic compounds with extraordinary high stereocontrol.

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Supplementary Material Available: Complete experimental details for the reactions described (11 pages). Ordering information is given on any current masthead page.

Palladium-Mediated Macroheterocyclization. A Synthesis of Inandenin-12-one

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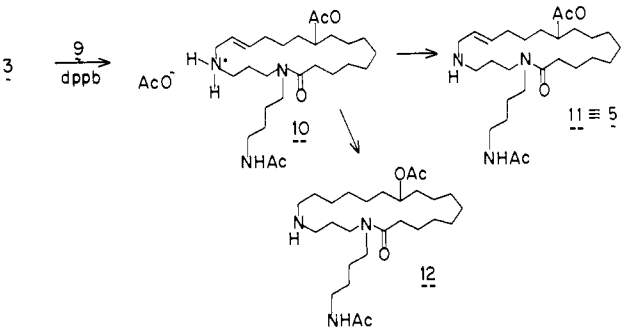
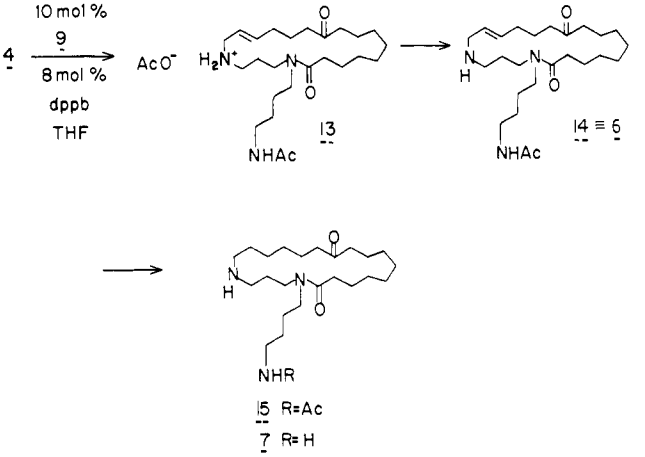
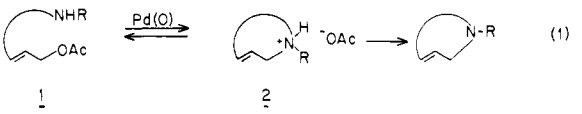
Increased attention focuses on large heterocyclic rings because of their ionophoric properties. Such properties may be responsible for much of the observed biological activity of naturally occurring macroheterocycles. Among the more interesting classes of macrocyclic amines are those derived from spermine and spermidine.[1] The synthetic approaches to these compounds have been limited up to the present, to a macrolactamization as the key ring-forming step.[2,3] The general advantages of transition-metal-templated macrocyclizations involving C–C bond formation such as in the case of palladium-mediated reactions[4] raises the question of the applicability of such transition-metal catalysts in forming a C–X bond where X is oxygen or nitrogen.[5,6] In the case of nitrogen, the initial cyclization is simply an isomerizaiton (**1** ⇌ **2**, eq 1). Since allylammonium salts are known substrates for Pd(O),[6b,7] this isomerization becomes an equilibration. Thus, the success of this approach depends upon both kinetics and thermodynamics.

Scheme I. Cyclization of 3

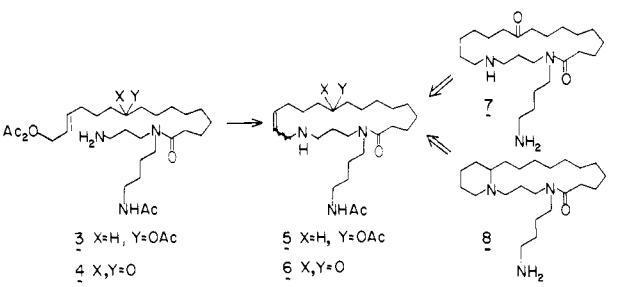


Scheme II. Synthesis of Inandenin-12-one





To explore this question, we examined the cyclizations of **3** and **4** since their cyclization products **5** and **6** represent possible common intermediates to the naturally occurring spermidine alkaloids inandenin-12-one (**7**)[8] and oncinotine (**8**)[2a,9]—a strategy that may mimic the biosynthetic pathway to **8**. Furthermore, since inandenin-12-one coexists with inandenin-13-one and this mixture



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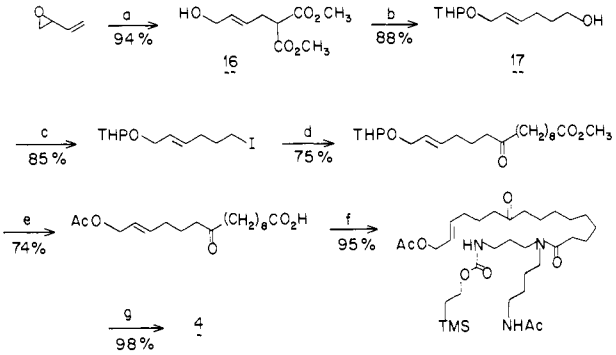
Scheme III. Synthesis of Cyclization Substrate 4[h]



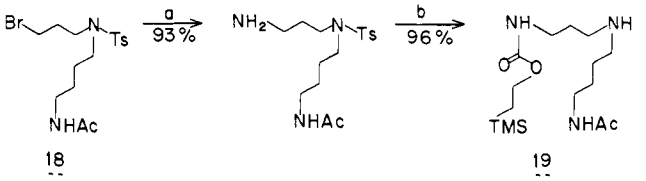
[a] $CH_2(CO_2CH_3)_2$, $(Ph_3P)_4Pd$, THF, 25 °C. [b] (i) DHP, TsOH, CH_2Cl_2, 0 °C; (ii) KOAc, Me_2SO, 140 °C; (iii) $LiAlH_4$, ether, 25 °C. [c] (i) MsCl, $(C_2H_5)_3N$, CH_2Cl_2, 0 °C; (ii) NaI, CH_3COCH_3, room temperature. [d] (i) t-C_4H_9Li, ether, −78 °C; $OHC(CH_2)_8CO_2CH_3$;[12] (ii) Me_2SO, $(COCl)_2$, $(C_2H_5)_3N$, CH_2Cl_2, −78 °C.[13] [e] (i) Dowex 50-W-8, CH_3OH, room temperature;[14] (ii) NaOH, CH_3OH, room temperature; (iii) Ac_2O, C_5H_5N, room temperature then $NaHCO_3$, H_2O, THF. [f] 19, DCC, DMAP, CH_2Cl_2, room temperature.[15] [g] CF_3CO_2H, 0 °C then $NaHCO_3$, H_2O. [h] New compounds have been fully characterized spectrally and by determination of elemental composition by combustion analysis and/or high-resolution mass spectroscopy.

is inseparable, only synthesis can provide the pure substances.

Subjecting **3** (Scheme I) to 10 mol % $(Ph_3P)_4Pd$ (**9**) and 12 mol % 1,4-bis(diphenylphosphino)butane (dppb) in THF at 70 °C (0.017 M in substrate **3**) led to a virtually quantitative recovery of material that was further purified by reverse-phase HPLC to give **10** as a thick oil in 77% yield. The ^1H NMR spectrum showed the absorptions for NHAc and $^+NH_2$ at δ 7.1 (br s) and 9.6 (br s), respectively, and $C{=}CCH_2NH_2^+$, $CH_2NHC{=}O$ and $2XCH_2NC{=}O$ between δ 3.2 and 3.8; the mass spectrum showed the highest mass peak at m/e 479 (45%) corresponding to M−HOAc. The stereochemistry of the double bond was predominantly E (vinyl protons of major isomer at δ 5.50 and 5.84, J = 16 Hz) which reflected the ~10:1 E/Z ratio of olefin isomers of the starting material. None of the alternative regiosomer is detected. Simple neutralization freed the amine **11**; however, its lability induced us to reduce the double bond of **10** (H_2, 10% Pd/C, C_2H_5OH, 1 atm) and then neutralize ($NaHCO_3$, H_2O) to give **12**. The mass spectrum confirmed its monocyclic nature (m/e 481. 3881); the NMR spectrum now exhibited an absorption for 6 H between δ 3.10 and 3.47 for $CH_2NHC{=}O$ and $CH_2NCH_2C{=}O$, a 4 H multiplet between δ 2.44 and 2.67 for the $-CH_2NHCH_2-$, and the amine and amide NH at δ 6.19 and 6.46.

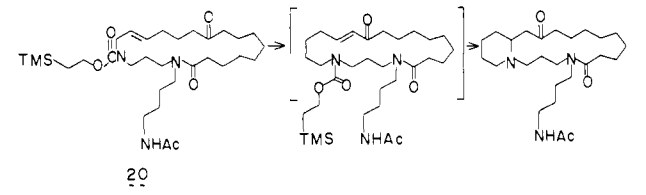
Subjecting the amino ketone **4** (Scheme II) to similar cyclization conditions showed a remarkable sensitivity to the ratio of dppb to **9**. When this ratio was >1, only elimination products formed; decreasing this ratio to <1 led smoothly to the isomer **13**, which is predominantly the E olefin isomer (δ 5.55 and 5.85, J = 16 Hz). In this case, the crude material was directly neutralized ($NaHCO_3$, H_2O) to give **14** in 80–89% yield after purification on an alumina column. The mass spectrum established its monocyclic nature (m/e 435.3459). The NMR spectrum showed absorptions for the amide NH at δ 6.37, for the three CH_2 groups bearing amide nitrogens at δ 3.14–3.46, and for the remaining CH_2 groups bearing nitrogen at δ 2.7 and 2.54. The rich infrared spectrum showed the expected absorptions for the ketone and amides (1705, 1670, 1630, 1520 cm^{-1}). This compound, like **11**, showed instability that could be resolved by hydrogenation to **15** as before (90% yield): IR 3460, 3360, 1705, 1670, 1630 cm^{-1}; NMR 6.28 (br s, 1 H, 3.15–3.51 (m, 6 H), 2.56 (m, 2 H), 2.51 (m, 2 H), 2.23–2.44 (m, 6 H), 2.16 (s, 1 H), 1.98, (s 3 H). Acidic methanolysis (4 N anhydrous HCl in CH_3OH, 120 °C) liberated pure inandenin-12-one (**7**) in 80% yield after purification on alumina. Its IR, NMR, and mass spectra compare favorably with those of the natural product mixture of the 12- and 13-one.

Scheme IV. Synthesis of Differential Spermidine



[a] (i) NaN_3, C_2H_5OH, reflux; (ii) $HS(CH_2)_3SH$, $(C_2H_5)_3N$, CH_3OH, room temperature.[17] [b] (i) $TMSCH_2CH_2OC(O)Cl$, CH_2Cl_2, DMAP, $(C_2H_5)_3N$, 0 °C → room temperature; (ii) Na, NH_3, THF, −78 °C.

Scheme V. Synthesis of 15-Oxoocinotin



The substrates are readily available as outlined in Scheme III for **4**; a very similar scheme was employed for the synthesis of **3**. The strategy in the formation of **17**, which utilizes the recently developed Pd-catalyzed neutral alkylation of vinyl epoxides[10] (i.e. in this case, alkylation of butadiene monoepoxide[11] to give **16**) proceeds in excellent yield, whereas attempts to make **17** via Claisen rearrangements failed. This step determines the olefin stereochemistry, which is 10:1 E:Z. Since this stereochemistry was irrevelant to the overall synthesis, this mixture was employed for further work. The differentiated spermidine unit **19**[2b,16] was readily obtained from the bromide **18** as outlined in Scheme IV.

This new cyclization approach provided a 21-membered ring in nearly quantitative crude yields in a highly chemo-, regio-, and stereoselective fashion. Thus, both kinetics and thermodynamics favor the macrocycle. This new cyclization may be a useful tool in evaluating the thermodynamic parameters associated with large rings. In addition, it constituted an efficient total synthesis of inandenin-12-one in 23.3% overall yield from butadiene monoepoxide. Preliminary experiments suggest that double bond isomerization in **20** with a mixture of rhodium chloride[18] and **9** is accompanied by cyclization to give the acetamide of 15-oxoocinotin (Scheme V). Thus, the introduction of the double bond required for the palladium-mediated cyclization also provides enhanced and useful synthetic versatility. Most importantly, this cyclization approach appears to be a useful entry to macroheterocycles.

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