HETEROCYCLES, Vol. 88, No. 2, 2014, pp. 1519 - 1526. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 27th June, 2013, Accepted, 14th August, 2013, Published online, 21st August, 2013
DOI: 10.3987/COM-13-S(S)54

IODOETHERIFICATION OF CONFORMATIONALLY RESTRICTED DIENYL ALCOHOLS: UNEXPECTED FORMATION OF OXOCENES BY 8-*ENDO*-MODE OXACYCLIZATIONS

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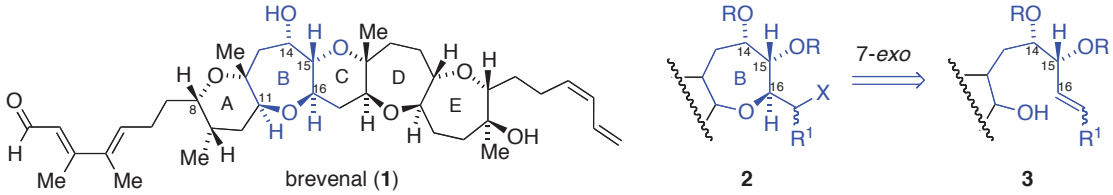
Abstract – Iodine-promoted oxacyclizations of a family of conformationally restricted dienyl alcohols consistently afford oxocenes, arising from 8-*endo*-mode cyclizations.

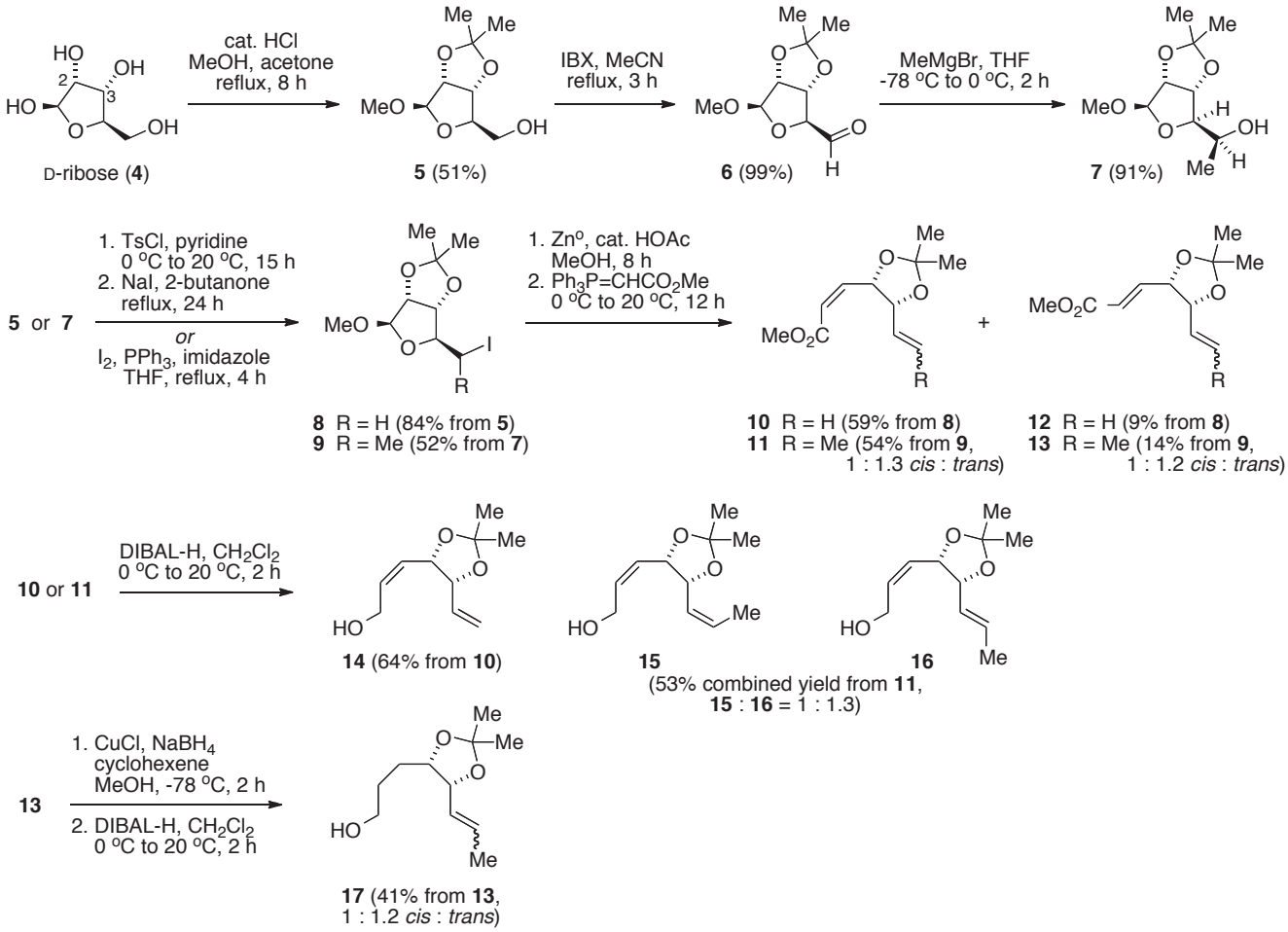
Fused polycyclic ether marine natural products exhibit a common *trans,syn,trans*-stereochemical motif with considerable variation in ring sizes from five- to nine-membered rings, as well as the number of cyclic ether rings within the structure.[1] In addition to the hallmark structures of the brevetoxins, ciguatoxins, and maitotoxin, the pentacyclic natural product brevenal (**1**, Scheme 1) acts as a non-toxic competitive inhibitor of brevetoxins and ciguatoxin binding to sodium ion-channel receptors, counteracting the neurotoxic effects of exposure to the higher molecular weight polycyclic ethers.[2] In contrast to our previous efforts to construct fused polycyclic ethers by *endo*-mode cascade oxacyclizations of polyepoxides,[3-5] we have recently reported several cases of stereoselective six-membered ring ether (tetrahydropyran) formation from alkenyl diol cyclizations, with stereoinduction from an allylic oxygen substituent.[6] The literature records several cases favoring 7-*exo*-mode oxacyclizations of alkenyl alcohol and alcohol derivatives (silyl ethers, isoxazolines) to form seven-membered ring ethers (oxepanes),[7,8] but the effect of an allylic oxygen substituent on stereoinduction has not been described for this method of oxepane synthesis. Thus we sought to evaluate the oxacyclization behavior of alkenyl alcohol substrates corresponding to compound **2**, with an acetal-protected diol corresponding to a model system for the B ring of brevenal (Scheme 1).

Dedicated in celebration of the 77th birthday of Prof. Victor Snieckus.



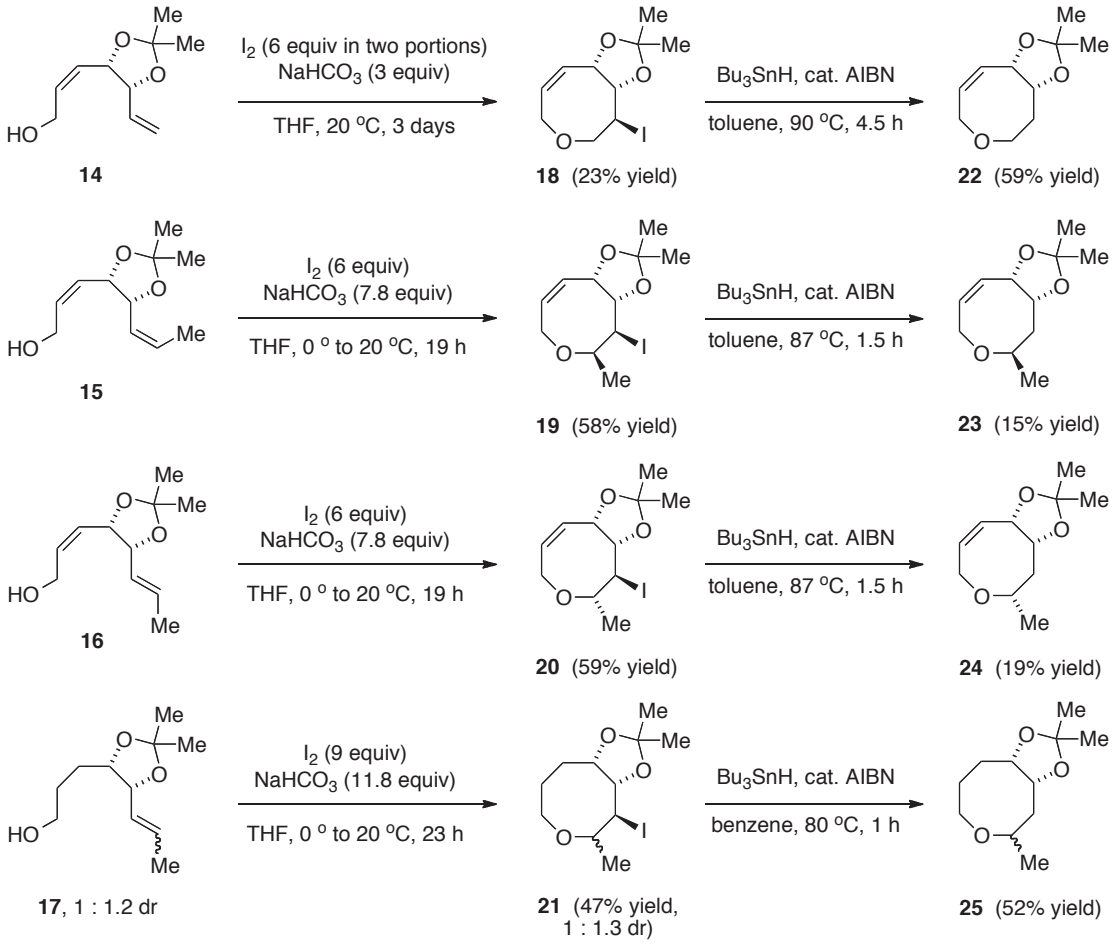
Scheme 1. Structure of brevenal (**1**), and proposed cyclization strategy for ring B

We envisioned that the *erythro*- stereochemistry of C14 and C15 in brevenal might arise from a carbohydrate starting material. Indeed a literature search revealed that compound **10** could be prepared from D-ribose (**4**, Scheme 2),[9] and DIBAL-H reduction provided the dienyl alcohol **14** substrate. The disubstituted dienyl alcohols **15** and **16** were prepared by adapting the established synthetic route from the secondary alcohol **7**.[10] The incorporation of the internal *cis*-alkenes in dienyl alcohols **14 - 16** limited free rotation in the tethers relative to compound **17**. For our purposes, the acetonide group not only isolated the primary alcohol in intermediate **5** for subsequent transformations, but also imparted additional conformational restriction in compounds **14** - **17** to favor cyclization. Although the methyl-substituted alkene diastereomers were inseparable as esters **11** or **13**, pure samples of the dienyl alcohols **15** and **16** could be isolated by chromatography on silver nitrate-impregnated silica gel.[11]

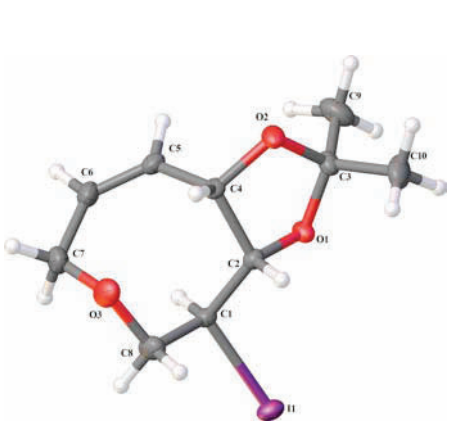


Scheme 2. Preparation of alkenyl alcohols **14** - **17** from D-ribose (**4**)

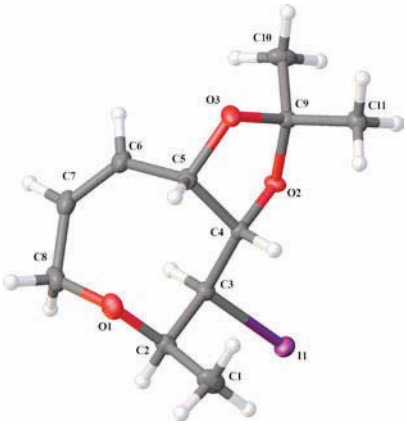
Iodocyclization of the dienyl alcohol **14** gave one major product, which upon crystallographic characterization was revealed as the oxocene **18** arising from the 8-*endo* cyclization mode (Schemes 3, 4).[12] In attempting to sterically block the 8-*endo* pathway, the *cis,cis*- and *cis,trans*-dienyl alcohols **15** and **16** were studied, but both compounds provided only the corresponding oxocenes **19** and **20**, as single diastereomers and without any evidence of oxepane formation.[13] The structural assignment for compound **19** was also confirmed by X-ray crystallography. Although compound **20** was not crystalline, the methyl doublets in the ^{1}H NMR spectra for each deiodination product **23** and **24** were consistent with 8-membered ring formation.[14] Moreover, deiodination of **19** and **20** produced different diastereomers, so we concluded by process of elimination that compound **20** must be the diastereomer of **19** at the position of the methyl substitution. To investigate if the *cis*-alkene in the tether was responsible for the unexpected regioselectivity, the hydroxyalkene **17** was studied (as a mixture of alkene isomers). However, iodocyclization also afforded the iodooxocane diastereomers **21**, with additional structural confirmation upon deiodination, again showing methyl doublets for each diastereomer of oxocane **25**.



Scheme 3. Iodocyclizations of alkenyl alcohols **14** - **17**



18



19

Scheme 4. Crystal structures of iodocyclization products

Although this study did not provide the desired oxepanes (seven-membered ring ether), the regio- and stereoselectivity of this process is notable, and might be exploited in future synthetic applications for oxocene natural products.[15] Current investigations towards achieving 7-*exo*-mode cyclizations are focused on changing the diol protective group, as the acetonide may be responsible for the 8-*endo* regioselectivity observed in this study.

EXPERIMENTAL

Representative Procedure for Iodine-promoted Oxacyclizations. The dienyl alcohol **15** (82 mg, 0.41 mmol) was dissolved in THF (4.1 mL), the solution was cooled to 0 °C, and solid $NaHCO_3$ (265 mg, 3.2 mmol) was added, followed by I_2 (624 mg, 2.5 mmol). The reaction mixture slowly warmed to room temperature over 19 h and was quenched with saturated aqueous $Na_2S_2O_3$ (30 mL). The aqueous layer was extracted with EtOAc (3 x 15 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude yellow material was purified by flash column chromatography (9:1 hexanes:EtOAc) to obtain iodooxocene **19** as a clear, colorless oil that solidified over time (77 mg, 58% yield).

(3a*S*,4*S*,9a*S*,*Z*)-4-Iodo-2,2-dimethyl-4,5,7,9*a*-tetrahydro-3*aH*-[1,3]dioxolo[4,5-*d*]oxocine (18): mp 65 - 67 °C. **^{1}H NMR** ($CDCl_3$, 600 MHz) δ 5.64 - 5.58 (H_a, m, 1H), 5.39 - 5.34 (H_b, H_c, m, 2H), 4.52 - 4.47 (H_d, m, 1H), 4.45 (H_e, ddd, J_1 = 5.0 Hz, J_2 = 10.5 Hz, J_3 = 12.5 Hz, 1H), 4.25 (H_f, dd, J_1 = 5.8 Hz, J_2 = 10.5 Hz, 1H), 4.03 (H_g, t, J = 12.5 Hz, 1H), 3.89 - 3.84 (H_h, m, 1H), 3.75 (H_i, dd, J_1 = 5.0 Hz, J_2 = 12.5 Hz, 1H), 1.50 (s, 3H), 1.41 (s, 3H). **^{13}C NMR** ($CDCl_3$, 150 MHz) δ 129.9, 129.8, 107.4, 81.9, 76.9, 76.5, 71.9, 28.1, 26.7, 26.2. **FT-IR** (neat from a CH_2Cl_2 solution, the compound solidified upon standing, cm^{-1}): 2986, 2918, 1380, 1368, 1262, 1248, 1222, 1164, 1106, 1081, 1055, 872, 738, 705 cm^{-1}. **HRMS** Calcd for $C_{10}H_{16}O_3I_1$ $(M+H)^+$: 311.01387, found 311.01466. **$[\alpha]_D^{25}$** +17.9 (*c* 0.6, $CHCl_3$). Single

crystals of compound **18** were obtained by slow evaporation of $CDCl_3$. A suitable crystal was selected and mounted on an Apex2_Mo diffractometer. The crystal was kept at 173 K during data collection. Using Olex2, the structure was solved with the Superflip structure solution program using Charge Flipping and refined with the ShelXL refinement package using least squares minimization (SHELXL-97, Sheldrick, 2008).[16] Crystal Data for $C_{10}H_{15}IO_3$ (M = 310.12): monoclinic, space group $P2_1$, a = 7.9870(8) Å, b = 9.0616(9) Å, c = 8.3508(8) Å. Tables of structural parameters are provided in the supporting information. Deposition number CCDC-946585 for compound **18**. Free copies of the data can be obtained via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK; Fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).

(3a*S*,4*S*,5*R*,9a*S*,*Z*)-4-Iodo-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3*aH*-[1,3]dioxolo[4,5-*d*]oxocine (19): mp 82 - 84 ºC; **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.54 (ddd, J = 12.0, 5.4, 4.2 Hz, 1H), 5.36 (ddd, J = 12.0, 6.0, 4.8 Hz, 1H), 5.28 (ddd, J = 6.0, 5.4, 2.4 Hz, 1H), 4.55 (dd, J = 11.1, 4.5 Hz, 1H), 4.46 (ddd, J = 18.6, 4.8, 4.2 Hz, 1H), 4.29 (dd, J = 11.1, 5.2 Hz, 1H), 3.91 – 3.85 (m, 2H), 1.53 (d, J = 6.5 Hz, 3H), 1.48 (s, 3H), 1.39 (s, 3H); **^{1}H NMR** (600 MHz, C_6D_6) δ 5.39 (m, 2H), 4.97 (ddd, J = 13.2, 6.0, 2.4 Hz, 1H), 4.48 (dd, J = 11.1, 4.8 Hz, 1H), 4.36 (dd, J = 11.1, 6.0 Hz, 1H), 3.93 (ddd, J = 18.6, 4.8, 2.4 Hz, 1H), 3.53 (qd, J = 6.6, 4.6 Hz, 1H), 3.04 (ddd, 18.6, 4.8, 2.4 Hz, 1H), 1.45 (s, 3H), 1.41 (d, J = 6.6 Hz, 3H), 1.33 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 129.9 (2 carbons), 107.1, 80.5, 77.9, 76.1, 71.2, 29.3, 28.3, 26.6, 18.5. **HRMS** (APCI): m/z calcd. $C_{11}H_{18}O_3I$ (M+H$^+$) 325.02951, found 325.02930. **$[\alpha]_D^{25}$** +24.0 (c 1.00, $CHCl_3$). **FT-IR** (neat, cm^{-1}): 2990, 2932, 2889, 1454, 1434, 1368, 1268, 1246, 1222, 1158, 1101, 1077, 1059, 1028, 935, 879, 711, 652. Single crystals of compound **19** were obtained by slow evaporation of CH_2Cl_2. Crystallography was conducted as described above, except that the crystal was kept at 109.1 K during data collection. Crystal Data for $C_{11}H_{17}IO_3$ (M = 324.14): orthorhombic, space group $P2_12_12_1$, a = 7.4901(6) Å, b = 10.2210(8) Å, c = 15.9521(12) Å. Tables of structural parameters are provided in the supporting information. Deposition number CCDC-946586 for compound **19**.

(3a*S*,4*S*,5*S*,9a*S*,*Z*)-4-Iodo-2,2,5-trimethyl-4,5,7,9a-tetrahydro-3*aH*-[1,3]dioxolo[4,5-*d*]oxocine (20): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 5.61 (ddd, J = 11.8, 4.2, 2.7 Hz, 1H), 5.41 (ddd, J = 11.8, 2.6, 1.6 Hz, 1H), 5.33 (ddd, J = 6.3, 4.8, 2.4 Hz, 1H), 4.44 – 4.32 (m, 1H), 4.25 – 4.20 (m, 2H), 4.18 (ddd, J = 18.0, 3.4, 1.9 Hz, 1H), 4.12 (ddd, J = 18.1, 4.8, 2.6 Hz, 1H), 1.59 (d, J = 4.9 Hz, 3H), 1.48 (s, 3H), 1.40 (s, 3H); **^{1}H NMR** (600 MHz, C_6D_6) δ 5.47 – 5.36 (m, 2H), 5.04 (ddd, J = 13.2, 3.6, 2.4 Hz, 1H), 4.32 (dd, J = 10.2, 2.0 Hz, 1H), 4.14 – 4.05 (m, 2H), 3.68 (ddd, J = 18.0, 4.8, 2.4 Hz, 1H), 3.54 (ddd, J = 18.0, 4.8, 1.8 Hz, 1H), 1.46 (s, 3H), 1.32 (s, 3H), 1.26 (d, J = 6.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 131.4, 130.0, 107.3, 83.2, 77.5, 76.7, 62.0, 35.4, 28.3, 26.2, 17.7. **FT-IR** (neat, cm^{-1}): 2984, 283, 1376, 1247, 1218, 1165, 1080, 1048, 910, 866, 732, 694, 650. **$[\alpha]_D^{25}$** +14.8 (c 1.94, $CHCl_3$).

(3a*S*,4*S*,9a*S*)-4-Iodo-2,2,5-trimethylhexahydro-3*aH*-[1,3]dioxolo[4,5-*d*]oxocine (21), mixture of diastereomers at C5: **^{1}H NMR** (600 MHz, $CDCl_3$) δ 4.61 (dd, *J* = 11.4, 4.8 Hz, 1H), 4.35 – 4.22 (m, 6H), 4.04 (ddd, *J* = 13.8, 7.2, 6.6 Hz, 1H), 3.93 – 3.84 (m, 2H), 3.56 (ddd, *J* = 11.4, 4.5, 2.7 Hz, 1H), 3.32 (td, *J* = 11.6, 2.4 Hz, 1H), 3.26 (t, *J* = 12.2 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.80 – 1.69 (m, 3H), 1.69 – 1.61 (m, 4H), 1.60 (d, *J* = 6.5 Hz, 3H), 1.52 (d, *J* = 6.2 Hz, 3H), 1.43 (s, 6H), 1.36 (s, 3H), 1.36 (s, 3H). **^{13}C NMR** (150 MHz, C_6D_6) δ 105.83, 105.71, 83.02, 80.18, 79.67, 77.71, 77.45, 76.01, 68.48, 62.14, 34.85, 31.57, 30.58, 29.43, 29.17, 28.74, 26.52, 26.26 (2), 19.27, 18.63. **HRMS** (NSI): *m/z* calcd. $C_{11}H_{20}IO_3$ ($M+H^+$) 325.02951, found 325.02928. **FT-IR** (neat, cm^{-1}): 2984, 2932, 2877, 1451, 1369, 1220, 1168, 1080, 1037, 961, 939, 866, 826, 753, 706. **$[\alpha]_D^{25}$** +10.8 (*c* 0.80, $CHCl_3$).

ACKNOWLEDGEMENTS

This material is based upon work supported by the National Science Foundation under grant CHE-1151304. A.N.R.A. thanks MICINN for supporting her research fellowship at Emory University.

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12. The corresponding selenium-promoted cyclization of **14** (PhSeNPhth, CSA, CH_2Cl_2) provided the phenylselenium analog of **18** in low yield, which provided the oxocene **22** upon radical deselenylation.
13. The iodocyclization processes described herein required a considerable excess of iodine to maximize conversion of **14** - **17** to the corresponding cyclic ethers. The yields obtained for compounds **19** - **21** were obtained only when the molar amount of sodium bicarbonate exceeded the amount of iodine used.
14. We did not find any products from transannular cyclization onto the cyclic alkene in the radical deiodinations. The deiodination transformations were conducted primarily to confirm the ring sizes for the iodocyclization products, thus we did not attempt to optimize the yields for compounds **23** and **24**. The yield of the compound **25** (from deiodination of the saturated cyclic ether **21**) was

notably higher, but a lower boiling solvent (benzene instead of toluene) was used for this transformation.

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