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4,5-Didehydro-7-silyloxymethyl-2-oxepanone and formal total syntheses of Hagen's gland lactones and *trans*-kumausynes

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Abstract—A concise and enantiospecific route to the 2,6-dioxabicyclo[3.3.0]octan-3-one ring system from commercially available (*R*)-(+)- and (*S*)-(−)-glycidols is described. The key features involve ring closing metathesis to construct the 7-substituted-4,5-dehydro-2-oxepanone and its base-catalyzed single-step rearrangement into the 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton. Using this strategy, formal total syntheses of (7*R*)-*cis*-Hagen's gland lactones and (+)- and (−)-*trans*-kumausynes have been achieved.

The 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton is present in a number of natural products possessing diverse biological activities. It serves also as a useful synthon for several other compounds of this type. In particular, plakortones, **1**, represent a new family of drugs of substantial pharmacological interest that are relevant in the correction of cardiac relaxation irregularities and exhibit in vitro cytotoxic activity on the murine fibrosarcoma cell line.[1] (+)-Goniofufurone, **2**, is an antitumor styryl-lactone.[2] These lactones have generated considerable synthetic interest.[3,4] The Hagen's glands of some parasitic wasps contain fragrant volatile biological control agents that are rich in γ-lactones including bicyclic materials **3a** and **3b**.[5] There has been some interest in the study of their biological roles.[6]

The related kumausynes **4** and kumausallene **5** are structurally diverse nonisoprenoid compounds, isolated from the red algae of the genus Laurencia,[7] which belong to a growing family of halogenated natural products.[8] These materials have been demonstrated to exhibit diverse biological properties such as antitumor, antimicrobial, immunosuppressant, antifeedant, and pesticidal activity. Several syntheses of **4**[9] and **5**[10] have appeared. Most of these approaches are based on a unified strategy that involves the 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton as the single most important intermediate (Fig. 1).[5e,11]

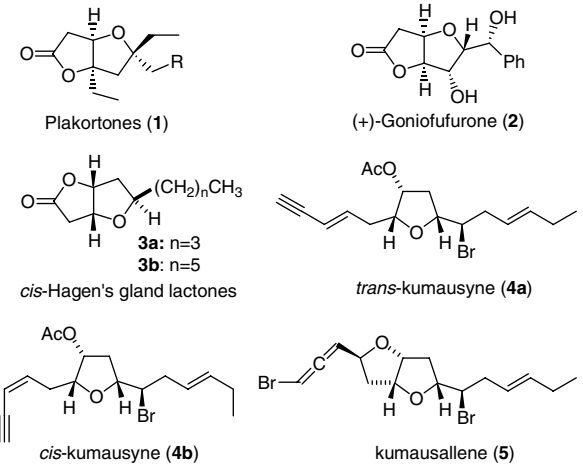

Figure 1. Biologically active natural products containing the 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton.

The unique structural features and a wide range of biological activities of the above natural products have stimulated considerable synthetic interest aimed toward the synthesis of the 2,6-dioxabicyclo[3.3.0]octan-3-one skeleton. We have previously reported a racemic synthesis of this bicyclic framework starting from 2-carbomethoxycyclohexanone.[12] This protocol, however, was poor yielding. We report, herein, a new concise and

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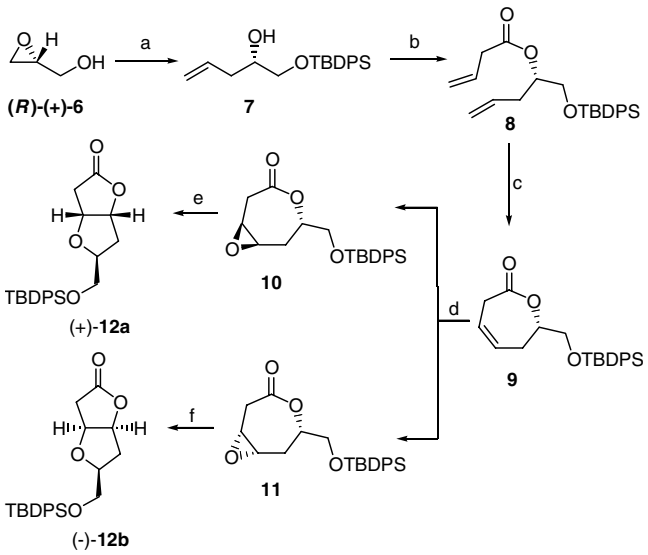


Scheme 1. Reagents and conditions: (a) (i) TBDPSCl, imidazole, CH_2Cl_2, 0–25 °C, 3 h, 99% and (ii) vinylmagnesium bromide, Cu_2I_2, THF, −20 °C, 45 min, 95%. (b) vinylacetic acid, DCC, DMAP, CH_2Cl_2, 0–25 °C, 6 h, 89%; (c) 5 mol % of Grubbs' second generation catalyst, CH_2Cl_2, 25 °C, 10 h, 72%. (d) epoxidation; (e) DBU, $CHCl_3$, 0–25 °C, 6 h, 85% and (f) K_2CO_3, DMF, 25 °C, 6 h, 90%.

enantiospecific route to this skeleton from commercially available chiral glycidols by exploiting ring closing metathesis[13] to construct the 7-substituted-4,5-didehydro-2-oxepanone followed by a base-promoted single-step rearrangement to the 7-substituted-2,6-dioxabicyclo[3.3.0]octan-3-one skeleton to achieve formal total syntheses of (7*R*)-*cis*-Hagen's gland lactones and (+)- and (−)-*trans*-kumausynes.

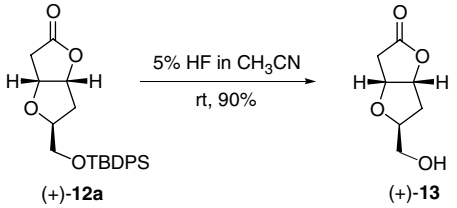
The syntheses of 7-*tert*-butyldiphenylsilyloxymethyl-2,6-dioxabicyclo[3.3.0]octan-3-ones, (+)-**12a** and (−)-**12b**, are illustrated in Scheme 1. It commences with imidazole-promoted protection of the carbinol function in (*R*)-(+)-glycidol **6** with TBDPSCl, followed by a reaction with vinylmagnesium bromide (1.0 M in THF) in the presence of Cu_2I_2[14] to furnish **7** in 94% yield over two steps. The oxirane ring cleavage took place with full regiocontrol, giving a single product, as shown, in accord with the literature.[14] Acylation with vinylacetic acid in the presence of DCC and DMAP gave, after chromatographic purification, the ring closing metathesis precursor **8** in 89% yield. RCM of **8**, catalyzed by Grubbs' second generation catalyst, proceeded well under dilute conditions and the desired seven-membered ring lactone **9** was isolated in 72% yield.

The exposure of **9** to *m*-CPBA in CH_2Cl_2 at 0 °C furnished an easily separable mixture of oxiranes **10** and **11** in a 2:1 ratio and a combined 85% yield. This ratio changed to 1:1.5 and 1:3 on oxidation with, respectively, acetone dioxirane[15] and the oxirane formed from Shi's diester.[16] These oxidation results are collected in Table 1. The treatment of **11** with anhydrous K_2CO_3 in DMF[12] generated (−)-**12b** in 90% yield after chromatographic purification. However, under these conditions, **10** did not undergo a complete conversion into (+)-**12a**. On screening suitable conditions for this transformation, DBU in $CHCl_3$ offered the best result and (+)-**12a** was formed in 85% yield after chromatographic purification.

Table 1. Diastereoselectivity in the epoxidation of **9** with different reagents

Epoxidation reagents	Products	Yield (%) (**10**:**11**)[a]
m-CPBA	**10** + **11**	85 (2:1)
Oxone®/acetone	**10** + **11**	90 (1:1.5)
Oxone®/Shi's diester	**10** + **11**	85[b] (1:3)

[a] Isolated yields. The diastereomeric ratios were determined from integration of the relative ^{1}H NMR signals.
[b] Yield is based on 55% conversion.



Scheme 2. Transformation of (+)-**12a** into (+)-**13**.

The spectral data of (−)-**12b** and its optical rotation were consistent with those reported in the literature.[11d] The elaboration of (−)-**12b** into (+)-*trans*-kumausyne has been reported previously by Boukouvalas et al.[11c] The diastereomer (+)-**12a** gave alcohol (+)-**13** on cleavage of the TBDPS-ether with 5% HF in CH_3CN in 90% yield, Scheme 2. The spectral data of (+)-**13** were in agreement with those reported by Mereyala and Gadikota.[5d] The elaboration of (+)-**13** into (7*R*)-*cis*-Hagen's gland lactones has also been reported previously by these authors.[5d]

Following a similar protocol with (*S*)-glycidol, we have achieved the syntheses of (−)-**12a** and (+)-**12b**. The spectral data of (+)-**12b** and its optical rotation were in agreement with those reported in the literature.[5d] The elaboration of (+)-**12b** into (−)-*trans*- kumausyne has been reported previously by Osumi and Sugimura.[11a] The enantiomeric purities of (+)-**12a**, (−)-**12a**, (+)-**12b**, and (−)-**12b** were assessed by chiral HPLC (chiralcel-ODH) using a 97.5:2.5 mixture of *n*-hexanes and *i*-PrOH as solvent.

Mereyala and Gadikota have synthesized (+)-**12b** during a formal total synthesis of (−)-*trans*-kumausyne over 10 steps in a 10.9% overall yield.[5d] The synthesis of (+)-**12b** by Osumi and Sugimura proceeded in 11 steps in 11.3% overall yield.[11a] The synthesis of (+)-**12b** by Boukouvalas et al. required only six steps and proceeded in a 30.9% overall yield[11c] and, thus, from comparable to the present protocol. Lee et al. have synthesized the corresponding aldehyde (replace CH_2OSiPh_2t-Bu by CHO) over thirteen steps in a 10.7% overall yield.[11b] Gadikota et al. have also achieved the synthesis of (−)-**12b** in a projected formal total synthesis of (+)-*trans*-kumausyne over 12 steps in 20.3% overall yield.[11d] Pradilla et al.

have prepared the alcohol corresponding to (−)-**12b** in five steps; the overall yield, however, was only 6.6%.[9c]

Mereyala and Gadikota have prepared (+)-**13** for the synthesis of (7*R*)-*cis*-Hagen's gland lactones in a 12.8% overall yield in nine steps.[5d] Our synthesis proceeds in seven steps and generates (+)-**13** in a 27% overall yield. The synthesis of (−)-**12a**, a potential candidate for the synthesis of (7*S*)-Hagen's gland lactones, has not been reported previously.

In summary, facile enantiospecific syntheses of 7-*t*-butyldiphenylsilyloxymethyl-2,6-dioxabicyclo[3.3.0]octan-3-ones, (+)-**12a**, (−)-**12a**, (+)-**12b**, and (−)-**12b** have been achieved from commercially available chiral glycidols in 30%, 31%, 35% and 36% overall yields, respectively, over six steps. The yields of (+)-**12a** and (−)-**12a** are based on the oxidation results obtained from *m*-CPBA and those of (+)-**12b** and (−)-**12b** are based on the oxidation results obtained from application of the dioxirane formed from Shi's diester.

The key features of our strategy are ring closing metathesis to construct the 7-*t*-butyldiphenylsilyloxymethyl-4,5-didehydro-2-oxepanone **9** and a base-promoted one-step rearrangement of 7-*t*-butyldiphenylsilyloxymethyl-4,5-epoxy-2-oxepanones **10/11** into the requisite bicyclic skeleton. We have demonstrated the utility of this approach for the formal total syntheses of (7*R*)-*cis*-Hagen's gland lactones and (+)- and (−)-*trans* kumausynes herein.[17] A similar application to the synthesis of goniofufurone is currently under investigation.

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17. Spectral data of *tert*-butyldiphenylsilyl ether of (*S*)-glycidol: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.67 (m, 4H), 7.44–7.36 (m, 6H), 3.86 (dd, $J = 12.0$, 3.2 Hz, 1H), 3.70 (dd, $J = 12.0$, 4.9 Hz, 1H), 3.14–3.10 (m, 1H), 2.73 (dd, $J = 5.1$, 4.2 Hz, 1H), 2.60 (dd, $J = 5.1$, 2.7 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.59, 135.54, 133.3, 129.7, 127.7, 64.3, 52.3, 44.4, 26.7, 19.2. IR (neat) 2931, 1467, 1110, 823, 704 cm^{-1}. Anal. Calcd for $C_{19}H_{24}O_2Si$: C, 73.03; H, 7.74. Found: C, 72.90; H, 7.80.
Spectral data of (*S*)-1-(*tert*-butyldiphenylsilyloxy)-4-penten-2-ol (**7**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.65 (m,4H), 7.45–7.36 (m, 6H), 5.82–5.75 (m, 1H), 5.09–5.03 (m, 2H), 3.80–3.75 (m, 1H), 3.67 (dd, $J = 10.2$, 3.9 Hz, 1H), 3.55 (dd, $J = 10.2$, 6.8 Hz, 1H), 2.26–2.22 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.5, 134.3, 133.1, 129.7, 129.4, 127.7, 127.5, 117.3, 71.2, 67.3, 37.5, 26.8, 19.2. IR (neat) 3071, 2931, 1428 cm^{-1}. Anal. Calcd for $C_{21}H_{28}O_2Si$: C, 74.07; H, 8.29. Found: C, 74.10; H, 8.30.
Spectral data of (*S*)-1-(*tert*-butyldiphenylsilyloxy)pent-4-en-2-yl-3-butenoate (**8**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.64 (m, 4H), 7.45–7.35 (m, 6H), 5.94–5.86 (m, 1H), 5.75–5.68 (m, 1H), 5.17–5.03 (m, 5H), 3.74–3.67 (m, 2H), 3.11–3.00 (m, 2H), 2.48–2.42 (m, 1H), 2.39–2.32 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.9, 135.6, 135.5, 133.3, 133.2, 130.3, 129.9, 129.6, 127.6, 118.4, 117.9, 73.7, 64.3, 39.2, 35.0, 26.7, 19.2. IR (neat) 3073, 2933, 1738, 1428 cm^{-1}. Anal. Calcd for $C_{25}H_{32}O_3Si$: C, 73.49; H, 7.89. Found: C, 73.40; H, 7.90.
Spectral data of (*S*)-7-((*tert*-butyldiphenylsilyloxy)methyl)-4,5-dehydro-oxepan-2-one (**9**). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.64 (m, 4H), 7.44–7.36 (m, 6H), 5.73–5.68 (m, 1H), 5.54–5.50 (m, 1H), 4.73–4.67 (m, 1H), 3.84 (dd, $J = 10.8$, 5.6 Hz, 1H), 3.67 (dd, $J = 10.8$, 6.1 Hz, 1H), 3.60 (dd, $J = 16.6$, 3.0 Hz, 1H), 3.01 (dd, $J = 16.6$, 8.5 Hz, 1H), 2.57–2.52 (m, 1H), 2.42–2.34 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 135.6, 133.0, 129.9, 128.8, 127.8, 127.7, 118.6, 65.5, 33.9, 32.2, 29.7, 26.8, 19.2. IR (neat) 3042, 2932, 1742, 1428 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_3Si$: C, 72.59; H, 7.42. Found: C, 72.45; H, 7.35.
Spectral data of **10**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.65 (m, 4H), 7.46–7.37 (m, 6H), 4.16–4.11 (m, 1H), 3.79 (dd, $J = 11.2$, 5.4 Hz, 1H), 3.69 (dd, $J = 10.7$, 5.4 Hz, 1H), 3.31–3.27 (m, 1H), 3.22–3.21 (m, 1H), 3.14 (dd, $J = 15.4$, 8.1 Hz, 1H), 2.91 (dd, $J = 15.4$, 2.4 Hz, 1H), 2.51 (d, $J = 16.1$ Hz, 1H), 2.20–2.13 (ddd, $J = 16.1$, 11.2, 2.4 Hz, 1H), 1.06 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6, 135.6, 132.8, 129.9, 127.8, 73.6, 65.0, 52.6, 48.6, 34.1, 30.4, 26.8, 19.2. IR (KBr) 2928, 2850, 1730, 1426, 1109 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.60; H, 7.10.
Spectral data of **11**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.66$–7.64 (m, 4H), 7.47–7.38 (m, 6H), 4.52–4.47 (m, 1H), 3.78 (dd, $J = 10.5$, 5.1 Hz, 1H), 3.58 (dd, $J = 10.5$, 6.6 Hz, 1H), 3.39–3.22 (m, 4H), 2.39–2.25 (m, 2H), 1.07 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 135.5, 132.82, 132.77, 130.0, 127.8, 76.1, 65.4, 52.6, 50.7, 35.4, 28.8, 26.8, 19.2. IR (KBr) 2928, 2857, 1741, 1426, 1110 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.56; H, 7.15.
Spectral data of (1*R*,5*R*,7*S*)-7-*tert*-butyldiphenylsilyloxymethyl-2,6-dioxabicyclo[3.3.0]octan-3-one, (+)-**12a**. $[\alpha]_D^{25}$ +24.7 (*c* 1.0, $CHCl_3$) [lit.[5e] $[\alpha]_D^{25}$ +25.0 (*c* 0.8, $CHCl_3$)], ee 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66–7.62 (m, 4H), 7.43–7.35 (m, 6H), 5.11 (dd, $J = 4.6$ Hz, 1H), 4.82–4.79 (m, 1H), 4.31–4.26 (m, 1H), 3.80 (dd, $J = 11.0$, 3.4 Hz, 1H), 3.63 (dd, $J = 11.0$, 3.6 Hz, 1H), 2.71–2.69 (m, 2H), 2.34 (dd, $J = 14.2$, 6.4 Hz, 1H), 2.21–2.14 (m, 1H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.8, 135.5, 133.1, 129.81, 129.76, 127.7, 85.1, 79.4, 78.6, 65.4, 36.9, 34.4, 26.8, 19.2. IR (KBr) 2927, 1785, 1429, 1110 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.70; H, 7.10.
Spectral data of (1*S*,5*S*,7S)-7-*tert*-butyldiphenylsilyloxymethyl-2,6-dioxabicyclo[3.3.0]octan-3-one, (−)-**12b**. $[\alpha]_D^{25}$ –25.8 (*c* 0.67, $CHCl_3$) [lit.[14d] $[\alpha]_D^{25}$ –26.0 (*c* 1.5, $CHCl_3$)], ee 97.4%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.64 (m, 4H), 7.45–7.36 (m, 6H), 5.03–5.01 (m, 1H), 4.59–4.57 (m, 1H), 4.15–4.12 (m, 1H), 3.76–3.67 (m, 2H), 2.71 (d, $J = 4.1$ Hz, 2H), 2.40–2.33 (m, 1H), 2.24–2.18 (m, 1H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.2, 135.6, 133.33, 133.26, 129.7, 127.7, 84.3, 80.6, 78.9, 65.5, 36.4, 34.6, 26.8, 19.2. IR (KBr) 3071, 2928, 1783, 1428, 1113 cm^{-1}. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.60; H, 7.15.
Spectral data of (−)-**12a**. The ^{1}H and ^{13}C spectral data were identical to that of (+)-**12a**. $[\alpha]_D^{25}$ −25.0 (*c* 0.8, $CHCl_3$), ee 98%. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66% H, 7.12. Found: C, 69.55; H, 7.10. Spectral data of (+)-**12b**. $[\alpha]_D^{25}$ +25.0 (*c* 0.7, $CHCl_3$), [lit.[5d] $[\alpha]_D^{25}$ +25.4 (*c* 0.8, $CHCl_3$)], ee 98%. The ^{1}H and ^{13}C spectral data were identical to that of (−)-**12b**. Anal. Calcd for $C_{23}H_{28}O_4Si$: C, 69.66; H, 7.12. Found: C, 69.50; H, 7.04.
Spectral data of (1*R*,5*R*,7*S*)-7-hydroxymethyl-2,6-dioxabicyclo[3.3.0]octan-3-one, (+)-**13**. $[\alpha]_D^{25}$ +41.5 (*c* 1.0, $CHCl_3$), [lit.[5d] $[\alpha]_D^{25}$ +41.7 (*c* 1.4, $CHCl_3$)], ee 98%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.15 (dd, $J = 4.6$ Hz, 1H), 4.85–4.83 (m, 1H), 4.32–4.26 (m, 1H), 3.86 (dd, $J = 12.0$, 2.7 Hz, 1H), 3.56 (dd, $J = 12.0$, 4.6 Hz, 1H), 2.81–2.67 (m, 2H), 2.32 (dd, $J = 14.2$, 5.6 Hz, 1H), 2.12–2.05 (m, 1H), 1.87 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 85.0, 79.0, 78.4, 63.3, 36.8, 33.8. IR (neat) 3367, 2925, 1750, 1040 cm^{-1}. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.10; H, 6.40.