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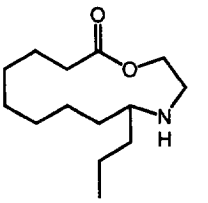
Synthesis of a Mexican Bean Beetle Azamacrolide Allomone via a Novel Lactam to Lactone Ring Expansion‡

Gordon W. Gribble* and Richard A. Silva

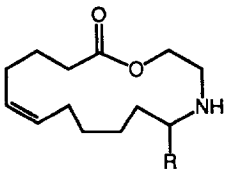
Department of Chemistry, Dartmouth College, Hanover, New Hampshire 03755

Abstract: The Mexican bean beetle (*Epilachna varivestis*) defensive secretion azamacrolide **1** has been synthesized via the novel ring expansion of N-hydroxyethyl lactam **12**, which was prepared in seven steps from cyclooctanone (**6**).

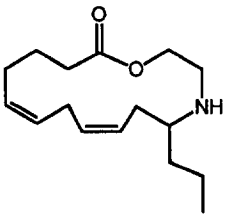
Azamacrolides **1-5** are a novel set of alkaloids produced by the pupa of the Mexican bean beetle (*Epilachna varivestis*) as a defensive secretion against ants.[1]



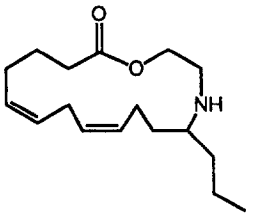
1 (0.20%)



2, R = *n*-Pr (epilachnene; 90.90%)
3, R = Et (norepilachnene; 0.25%)



4 (epilachnadiene; 8.55%)

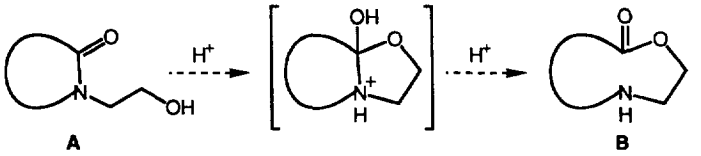


5 (homoepilachnene; 0.10%)

Although the major component of this allomone secretion is epilachnene (**2**), the saturated 9-*n*-propyl-10-azacyclododecan-12-olide (**1**) is more potent than **2** against black ants (*Larius niger*).[2] Rao has reported syntheses of all five of these azamacrolides in racemic form using a Yamaguchi macrolactonization [3] as the key step in this linear strategy.[2,4] As described in the accompanying Letter, Meinwald has also completed a synthesis of (±)-**1**.[5]

‡ Dedicated with deep affection to Professor Lloyd J. Dolby on the occasion of his 60th birthday.

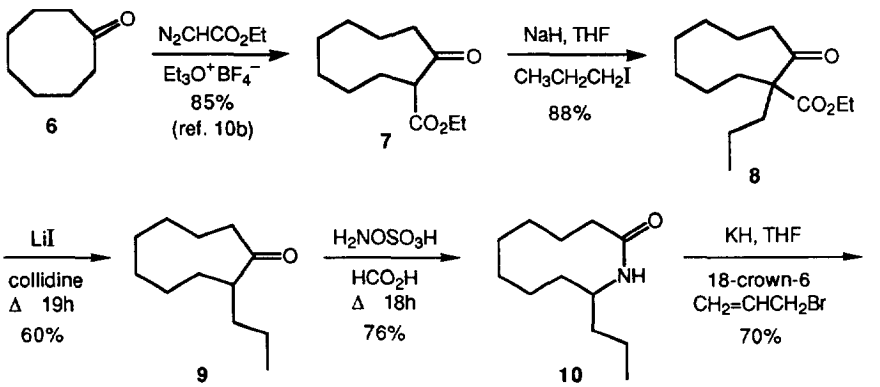
Our synthetic approach to these compounds hinged on the novel ring expansion of an *N*-hydroxyethyl lactam **A** to the corresponding azalactone **B**, as shown.[6] We felt that the driving force would be the relief of transannular ring strain in the present situation as well as protonation of the basic product.

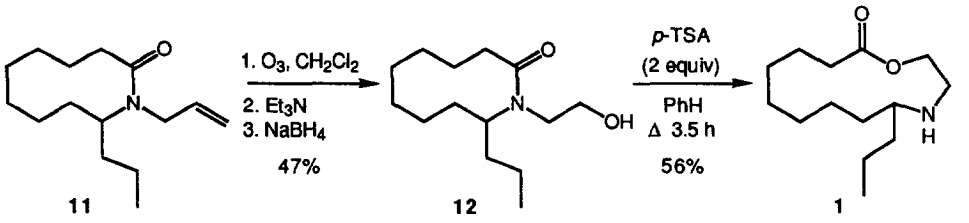


This internal lactam to lactone transformation is reminescent of Corey's internal translactonization[7] and Hesse's "zip-reaction" of *N*-aminoalkyl lactams and its several variations.[8,9] We now report the successful realization of this strategy.

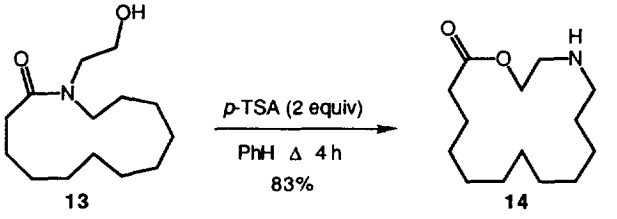
Our synthesis of racemic azamacrolide **1** is illustrated in the Scheme. Commercially available cyclooctanone (**6**) was transformed into the known 2-carboethoxycyclononanone (**7**) using the Mock ketone to β-ketoester homologation protocol.[10] Alkylation of the derived enolate of **7** with 1-iodopropane afforded **8**[11] in 88% yield. Decarboethoxylation of **8** by a standard method [12] gave 2-*n*-propylcyclononanone (**9**)[13] in modest yield. Although the (*E*)-oxime of **9** formed preferentially and underwent a Beckmann rearrangement to give the desired lactam **10**, the one-pot procedure of Olah[14] was particularly convenient in this regard and yielded **10**[15] in 76% yield. A small amount of the unwanted regioisomer could be detected in the crude product (^{13}C-NMR). Unfortunately, attempts to alkylate the amidate of lactam **10** directly with two-carbon electrophiles (ethylene oxide, $BrCH_2CH_2OTHP$) were unrewarding. However, alkylation of **10** with KH/allyl bromide gave **11**,[16] which upon ozonolysis and reduction gave the desired hydroxy lactam **12**[17] in 47% yield from **11**. Finally, treatment of **12** with *p*-toluenesulfonic acid (2 equiv) in refluxing benzene afforded (±)-**1** in 56% yield, identical to the natural allomone (IR, ^{1}H-NMR, ^{13}C-NMR, MS).[18]

Scheme





Interestingly, the analogous ring expansion of the 13-membered lactam **13** gave azamacrolide **14** in 83% yield. The higher yield of **14**, compared to that of **1**, perhaps reflects a higher relative entropy for the 16-membered ring in **14** than for the 13-membered ring in **1**.



Efforts both to optimize this synthetic sequence and to apply it to other members of this family of potential insect repellents are underway in our laboratory.

Acknowledgements. We are indebted to Professor William Mock for a very generous gift of **7**, and to Professor Jerrold Meinwald for spectra of natural **1** and for comparing it to our material, as well as for agreeing to joint publication.

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11. **8**: Bp 99-104 °C/0.15 Torr; IR (neat) 2946, 2929, 2871, 1728, 1706, 1465, 1200, 1126, 1026 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2 (m, 2H), 2.7 (tt, 1H), 2.2 (m, 2 H), 2.0-1.0 (m, 18 H), 0.9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 211.2, 172.6, 64.2, 61.1, 37.8, 33.5, 27.6, 25.3, 24.9, 23.9, 23.4, 20.1, 17.8, 14.7 ; MS *m/e* 254 (M^+), 225, 208, 166, 138, 115 (100), 95, 83; HRMS calcd for $C_{15}H_{26}O_3$: 254.1882. Found: 254.1881.
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13. **9**: Bp 98-100 °C/0.25 Torr; IR (neat) 2925, 1698, 1465, 1354, 1220, 1131 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.6 (m, 1H), 2.4 (m, 2H), 1.8-1.2 (m, 16H), 0.9 (t, 3 H), ^{13}C NMR ($CDCl_3$) δ 220.7, 53.4, 42.6, 35.7, 31.3, 26.3, 25.3, 25.1, 24.4, 21.0, 14.3; MS *m/e* 182 (M^+), 163, 153, 140, 123, 112, 98 (100); HRMS calcd for $C_{12}H_{22}O_1$: 183.1754. Found: 183.1748.
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15. **10**: Mp 132-133 °C; ^1H NMR ($CDCl_3$) δ 5.5 (s, 1H), 4.0 (m, 1H), 2.3 (t, 2H), 1.9-1.2 (m, 16 H), 0.9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 50.8, 37.8, 37.5, 30.3, 26.2, 24.6, 23.3, 19.6, 14.6; MS *m/e* 197 (M^+), 180, 168, 154, 137, 126, 98, 84, 72 (100); Anal. Calcd for $C_{12}H_{23}N_1O_1$: C, 73.04; H, 11.75; N, 7.10. Found: C, 72.85, H, 11.63; N, 7.06.
16. **11**: oil; IR (neat): 3430, 2914, 1727, 1627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.0 (m, 1H), 5.1 (m, 2H), 4.2 (t, 1H), 4.0-3.5 (m, 2 H), 2.9 (m, 1 H), 2.0 (m, 2H), 1.7-1.2 (m, 15 H), 1.9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.5, 135.7, 116.4, 57.5, 43.9, 37.1 33.5, 29.6, 25.9, 25.7, 21.3, 19.9, 19.7, 14.0 ; MS *m/e* 237(M^+), 222, 208, 194, 168, 152, 138, 112 (100); HRMS calcd for $C_{15}H_{27}N_1O_1$: 237.2093. Found: 237.2092.
17. **12**: oil; IR (neat) :3367, 2933, 1605, 1461, 1411, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.1 (m, 1H), 3.9-3.5 (m, 4 H), 3.3 (m, 1 H), 3.0 (m, 1H), 2.2 -1.3 (m, 14 H), 1.9 (t, 3 H) ;^{13}C NMR ($CDCl_3$) δ 177.5, 63.7, 57.5, 44.3, 37.1, 33.5, 29.6, 27.9, 25.8, 25.6, 21.3, 19.9, 19.7, 14.0 ; MS *m/e* 239 (M^+), 180, 168, 154, 137, 126, 98, 84, 72 (100); HRMS calcd for $C_{14}H_{27}N_1O_2$: 241.2044. Found: 241.2041.
18. **1**: oil; IR (neat) 3434, 3366, 2933, 1605, 1461, 1411, 1038, 500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2 (m, 2H), 3 (t, 1 H), 2.7 (m, 1 H), 2.5-2.3 (m, 3H), 1.7-1.2 (m, 17H), .9 (t, 3 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 64.6, 56.6, 46.7, 37.7 35.0, 32.2, 26.6, 26.0, 23.9, 22.5, 19.4, 14.6; MS *m/e* 241 (M^+), 226, 199, 198 (100), 170, 142, 116, 99, 97, 72, 55.

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