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Ethyl-Branched Aldehydes, Ketones, and Diketones from Caimans (*Caiman* and *Paleosuchus*; Crocodylia, Reptilia)

Karsten Krückert,[†] Birte Flachsbarth,[†] Stefan Schulz,*[,†] Ute Hentschel,[‡] and Paul J. Weldon[§]

Institut für Organische Chemie, Technische Universität Braunschweig, Hagenring 30, 38106 Braunschweig, Germany, Zentrum für Infektionsforschung, Universität Würzburg, Röntgenring 11, 97070 Würzburg, Germany, and Conservation and Research Center, Smithsonian Institution, 1500 Remount Road, Front Royal, Virginia 22630

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Secretions from the paracloacal glands of alligators (*Alligator* spp.) and caimans (*Caiman* spp., *Melanosuchus niger*, and *Paleosuchus* spp.) were examined by GC-MS. The secretions of the common caiman (*C. crocodilus*), the broad-snouted caiman (*C. latirostris*), the yacare caiman (*C. yacare*), the dwarf caiman (*P. palpebrosus*), and the smooth-fronted caiman (*P. trigonatus*) yielded a new family of 43 aliphatic carbonyl compounds that includes aldehydes, ketones, and β-diketones with an ethyl branch adjacent to the carbonyl group. The identification of these glandular components and the syntheses and stereochemical investigations of selected compounds are described.

Embedded in the cloacal walls of all modern crocodylians is a paired integumentary organ known as the paracloacal gland, a putative source of mating and/or nest-marking pheromones.[1] Chemical analyses of paracloacal gland lipids reveal esters, hydrocarbons, alcohols, and other compound classes, including many terpenoids.[2,4] Some compounds reported from the paracloacal glands of crocodylians are known from no other natural source. 11,12-Dihydrocembren-10-one, for example, is known only from the paracloacal gland of the Chinese alligator, *Alligator sinensis* (Alligatoridae), where in males this compound may comprise up to 30% of the volatile lipids.[3,4] Another unique ketone, 3,7-diethyl-9-phenylnonan-2-one (dianeackerone), occurs as the major volatile component of the secretions of adult African dwarf crocodiles, *Osteolaemus tetraspis* (Crocodylidae), but it is not present in immature specimens. Two isomers of dianeackerone—(3*S*,7*S*) and (3*S*,7*R*)—were observed among different individuals, in proportions ranging from <1:9 to >9:1, respectively.[5]

We have examined by GC-MS the paracloacal gland secretions of all extant species of the Alligatoridae, representing the genera *Alligator*, *Caiman*, *Melanosuchus*, and *Paleosuchus*. Our previous investigation of *Alligator* spp. and *Paleosuchus* spp. revealed eight novel acyclic mono- and sesquiterpene hydrocarbons exhibiting a rare trisubstituted 2,4-diene system.[4] We now report 43 novel ethyl-branched aldehydes, ketones, and diketones from among the following species: the common caiman, *C. crocodilus* (L.), which occurs from southern Mexico through Central America and northern South America (introduced in Puerto Rico and the United States); the broad-snouted caiman, *C. latirostris* (Daudin), which occurs in Bolivia, Paraguay, Uruguay, northern Argentina, and southeastern Brazil; the yacare caiman, *C. yacare* (Daudin), which occurs in Paraguay, northern Argentina, and southwestern Brazil; and the dwarf, *P. palpebrosus* (Cuvier), and the smooth-fronted caimans, *P. trigonatus* (Schneider), both of which occur throughout northern South America into Brazil. Our results further attest to the exotic chemistry of crocodylian skin glands.

Results and Discussion

GC-MS analysis of extracts of *Caiman* and *Paleosuchus* species revealed the presence of a number of components whose mass spectra are consistent with ketones. HR-MS showed the presence of one or two oxygen atoms in these compounds. Structure determinations by analysis of mass spectra, gas chromatographic retention indices, and verification of the derived structural proposals by syntheses led to the identification of heptan-3-one, 39 ethyl-branched mono- and diketones, and four ethyl-branched aldehydes.

* To whom correspondence should be addressed. Tel: +49 531 391 7353. Fax: +49 531 391 5272. E-mail: stefan.schulz@tu-bs.de.
[†] Technische Universität Braunschweig.
[‡] Universität Würzburg.
[§] Smithsonian Institution Front Royal.

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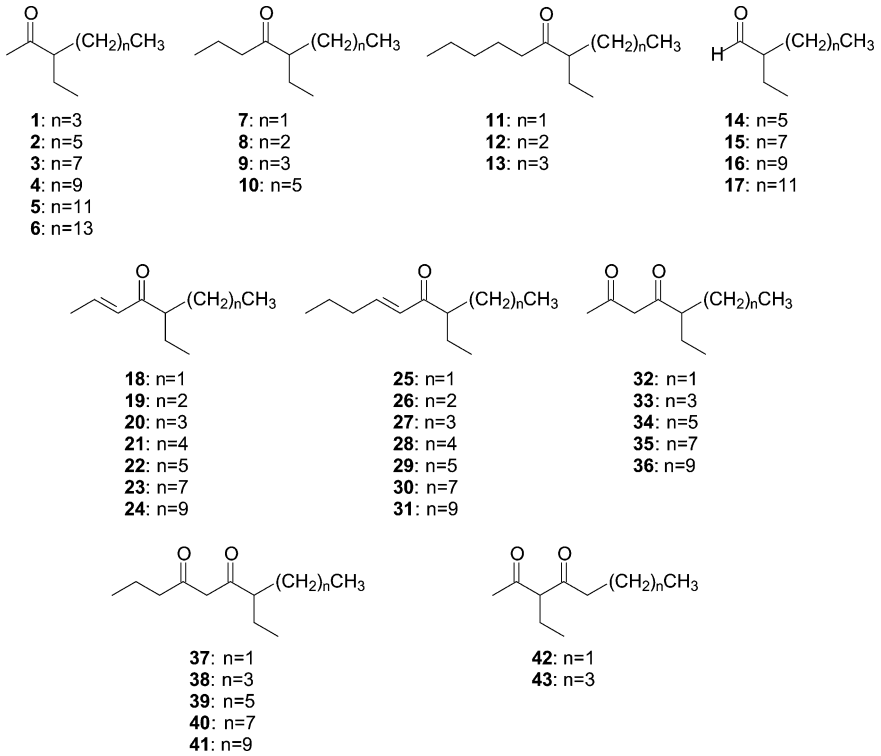
Chart 1



All 43 ethyl-branched compounds, which are new natural products, were observed in the *Caiman* species, while in *Paleosuchus* species only 14 of them occurred (Table 1). Neither aldehydes nor ketones were observed in either species of *Alligator* or *Melanosuchus niger*, the other alligatorids we investigated.

Saturated Ketones. Heptan-3-one and 13 saturated ethyl-branched ketones ranging in carbon-chain length from seven to 13 were observed among samples from all *Caiman* and *Paleosuchus* species. Each ketone possessed a carbonyl group with adjacent ethyl branch at C-2, C-4, or C-6. As an example, the identification of 5-ethylnonan-4-one (**9**) will be discussed. The molecular ion at *m*/*z* 170 corresponded to a molecular formula of $C_{11}H_{22}O$, which was determined by HR-GC-MS. The mass spectrum (Figure 1) showed α-cleavage ions at *m*/*z* 71 and 127. McLafferty rearrangement with the longer side chain produced *m*/*z* 114, which can lose 28 amu again to furnish *m*/*z* 86. Loss of a methyl group led to *m*/*z* 99. The McLafferty rearrangement to the other side of the keto group was disfavored (*m*/*z* 142). In the mass spectrum of these ketones it was generally observed that the McLafferty rearrangement preferentially took place on the ethyl-substituted side of the keto group. The base peak at *m*/*z* 57 ($C_4H_9^+$ by HR-GC-MS) could be explained by fragmentation of the C-5−C-6 bond. The charge resides exclusively at the alkyl fragment, because the resulting •CHR−C═O radical is stabilized by resonance. The opposite fragmentation with an alkyl radical and an α-carbonyl cation was disfavored because a positive charge at the α-C is very unstable due to the neighboring δ^+ charge at the carbon of the C═O bond (Figure 2). Diagnostic ions generated by this mechanism also were observed in the mass spectra of other caiman ketones, such as 5-ethyloctan-4-one (**8**, *m*/*z* 43), 5-ethylundecan-6-one (**12**, *m*/*z* 57), 5-ethylundecan-4-one (**10**, *m*/*z* 85), or 7-ethyltridecan-6-one (**13**, *m*/*z* 85). Compounds **7**−**10** were synthesized by alkylation of heptan-4-one with alkyl iodides, verifying the proposed structures.

Similar analysis of mass spectra, as well as gas chromatographic retention indices, revealed the presence of several other types of ethyl-branched ketones in the caiman secretions. They belong to three different classes in which the carbonyl group carries an α-ethyl branch. 3-Ethylalkan-2-ones occur as a bishomologous series ranging from C_7 to C_{17} (**1**−**6**). 5-Ethylalkan-4-ones are present with chain lengths from C_7 to C_9 and C_{11} (**7**−**10**). The keto group moves into the middle of the chain in 5-ethylundecan-6-one (**12**) and 7-ethyltridecan-6-one (**13**). The shorter 3-ethylnonan-4-one (**11**) also fits into this group. These assignments were corroborated by the synthesis of several reference compounds. 3-Ethylheptan-2-one (**1**) was synthesized by reaction of the Weinreb-amide of 2-ethylhexanoic acid with methylmagnesium iodide, while **12** was obtained by alkylation of undecan-6-one with ethyl iodide.

Saturated Aldehydes. A bishomologous series of four saturated ethyl-branched aldehydes ranging in carbon-chain length from eight to 14 were observed among our samples, sometimes in large amounts. Their mass spectra were dominated by a very strong ion at *m*/*z* 72, which is formed by McLafferty rearrangement (Figure 1). Also characteristic was the loss of 56 amu, presumably formed by expulsion of the ethyl branch and the C-2 and C-3 carbons from the molecular ion (Figure 2). An analogous M-42 ion could be observed in published spectra of 2-methylalkanals.[6] 2-Ethyldodecanal (**16**) was synthesized as a reference compound by alkylation of methyl dodecanoate with ethyl iodide, reduction with $LiAlH_4$, and final oxidation using pyridinium dichromate (PDC). Interestingly, the synthetic aldehyde was easily oxidized to the corresponding acid in air, while in the natural secretion the compound was stable over several months.

Unsaturated Ketones. Fourteen unsaturated ethyl-branched ketones ranging in carbon-chain length from seven to 17 were observed. The mass spectra of these unsaturated ketones resembled the spectra of the saturated analogues, but contained significant ions 2 amu less than those found in the latter. The spectrum of a compound related to **9** shows only a weak ion at *m*/*z* 57. The base peak at *m*/*z* 69 indicated the presence of an α,β-unsaturated carbonyl group at C-4. A McLafferty ion that easily loses $CH_3^•$ to form *m*/*z* 97 was present at *m*/*z* 112, indicating the ethyl branch. The mass spectrum allowed the assignment of 5-ethylnon-2-en-4-one (**20**) to this compound (Figure 1), which was synthesized from **9** by dehydration with iodosobenzoic acid (IBX).[7] The synthetic product confirmed the *E*-configuration of the natural compound. (*E*)-5-Ethylundec-2-en-4-one (**22**) was identified by comparison with synthetic material, while **18**−**24** showed similar fragmentation patterns and the expected gas chromatographic retention indices,

Table 1. Distribution of Aldehydes, Ketones, and Diketones in Male (M), Female, (F), and Unsexed Immatures (im) *Caiman* and *Paleosuchus* spp.[a]

		C. crocodilus			*C. latirostris*		*C. yacare*		*P. palpebrosus*			*P. trigonatus*		
	compound	M (3)	F (3)	im (7)	M (1)	F (5)	M (2)	F (5)	M (2)	F (2)	im (1)	M (2)	F (1)	im (4)
	heptan-3-one	0	0	0	1	0	0	0	0	0	0	0	0	0
1	3-ethylheptan-2-one	0	2	0	0	0	1	0	0	0	0	0	0	0
2	3-ethylnonan-2-one	1*	1	0	0	1	1	0	0	0	0	0	0	0
3	3-ethylundecan-2-one	0	1	1	0	0	0	0	0	0	0	0	0	1
4	3-ethyltridecan-2-one	0	1	1*	0	0	0	0	0	0	0	0	1	1
5	3-ethylpentadecan-2-one	1	2	1	0	1	1	1	0	0	0	1	0	1*
6	3-ethylheptadecan-2-one	0	1	0	0	0	0	0	0	0	0	0	0	0
7	3-ethylheptan-4-one	0	2	0	1	1	1	0	0	0	0	0	0	0
8	5-ethyloctan-4-one	0	1	0	1	0	0	0	0	0	0	0	0	0
9	5-ethylnonan-4-one	2*	3**	1	1*	2*	1**	4	1	1	0	0	0	0
10	5-ethylundecan-4-one	1	2	0	0	0	0	0	0	0	0	0	0	0
11	3-ethylnonan-4-one	1	3*	0	1	1	1*	0	1	0	0	1	1	0
12	5-ethylundecan-6-one	3*	3**	1	1	1	2**	4*	1*	1*	0	1	1	1
13	7-ethyltridecan-6-one	0	2	1	0	0	0	0	0	0	0	0	0	0
14	2-ethyloctanal	0	1	0	0	1	0	0	0	0	0	0	0	0
15	2-ethyldecanal	0	0	1	1	1*	0	0	0	0	0	0	0	0
16	2-ethyldodecanal	1*	2	1*	1*	5*	1	2*	0	0	0	0	1	1
17	2-ethyltetradecanal	3*	3**	1	1*	5*	1	4*	0	0	1	2	0	0
18	5-ethylhept-2-en-4-one	0	2	0	1	1*	1	0	0	0	0	0	0	0
19	5-ethyloct-2-en-4-one	0	0	0	1	0	0	0	1	0	0	0	0	0
20	5-ethylnon-2-en-4-one	2**	3**	1	1**	4**	2**	5*	1	2	1	2*	1*	1
21	5-ethyldec-2-en-4-one	2	0	0	1	0	0	0	0	0	0	0	0	0
22	5-ethylundec-2-en-4-one	1	3*	0	1*	4	1*	5*	0	0	1	0	0	0
23	5-ethyltridec-2-en-4-one	0	3*	0	0	1	0	4*	0	0	0	0	0	0
24	5-ethylpentadec-2-en-4-one	0	1	0	0	0	0	4	0	0	0	0	0	0
25	3-ethylnon-5-en-4-one	0	3*	0	1	1*	1*	1	0	1	1	0	0	1
26	7-ethyldec-4-en-6-one	2	1	0	1	1	0	0	0	0	0	0	0	0
27	7-ethylundec-4-en-6-one	3**	3**	1*	1**	5*	2*	5**	0	2	1	2*	1*	0
28	7-ethyldodec-4-en-6-one	2	0	0	1	0	0	0	0	0	0	0	0	0
29	7-ethyltridec-4-en-6-one	3**	3**	1*	1	4*	2*	5**	0	0	0	0	0	0
30	7-ethylpentadec-4-en-6-one	0	1*	0	0	0	0	0	0	0	0	0	0	0
31	7-ethylheptadec-4-en-6-one	0	1	0	0	1	1	1	0	0	0	0	0	0
32	5-ethylheptane-2,4-dione	0	2*	0	1	1	0	0	0	0	0	0	0	0
33	5-ethylnonane-2,4-dione	2	2**	0	1*	2*	1**	2	1	1	0	0	0	0
34	5-ethylundecane-2,4-dione	0	2	0	0	1	1*	0	0	0	0	0	0	0
35	5-ethyltridecane-2,4-dione	0	1	0	0	0	0	0	0	0	0	0	0	0
36	5-ethylpentadecane-2,4-dione	0	1	0	0	0	0	0	0	0	0	0	0	0
37	3-ethylnonane-4,6-dione	1	1**	0	0	0	1*	0	0	0	0	1	1	1
38	7-ethylundecane-4,6-dione	1	2**	0	0	2**	1*	1*	1	1**	1	1**	1*	1*
39	7-ethyltridecane-4,6-dione	1	2*	0	0	1	1*	1	0	0	0	0	0	0
40	7-ethylpentadecane-4,6-dione	0	1	0	0	0	0	0	0	0	0	0	0	0
41	7-ethylheptadecane-4,6-dione	0	1	0	0	0	0	0	0	0	0	0	0	0
42	3-ethylnonane-2,4-dione	0	1*	0	1	1*	0	0	0	0	0	0	0	0
43	3-ethylundecane-2,4-dione	0	1	0	0	0	0	0	0	0	0	0	0	0

[a] The number of individuals analyzed is indicated in parentheses. Numbers in columns denote the number of individuals possessing a compound; samples from immature were pooled and thus are represented by a single value. Asterisks indicate moderate (*) or high (**) abundance in one or more samples.

Table 2. Enantiomeric Composition of Different Ketones from Individual Samples Determined by GC with a Chiral 2,6-Di-*O*-methyl-3-*O*-pentyl-β-cyclodextrin in 50% OV 1701 Phase[a]

	9		**33**		**12**	
animal	*R* 20.23 min	*S* 20.79 min	*S* 30.65 min	*R* 31.71 min	*R* 41.24 min	*S* 41.94 min
Caiman crocodilus	92.3%	7.7%		100%	93.8%	6.2%
Caiman crocodilus	100%			100%	100%	
Caiman yacare	97.8%	2.2%		100%	85.4%	14.6%
Caiman latirostris	100%			100%	100%	
Paleosuchus trigonatus					100%	

[a] The gas chromatographic retention time of each enantiomer is shown in the table. The temperature program was as follows: 5 min at 40 °C, then 1 °C/min to 150 °C.

confirming their identity. A second class of unsaturated compounds seemed to be unsaturated analogues of the 7-ethylalkan-6-ones, because characteristic ions at *m*/*z* 97, 125, and 140 occurred in their mass spectra. (*E*)-7-Ethylundec-4-en-6-one (**27**) was synthesized by acylation of 1-pentene with 2-ethylhexanoyl chloride, verifying the proposed structure. Members of this class include the respective C_9-C_{13} compounds **25**−**29** as well as (*E*)-7-ethylpentadec-4-en-6-one (**30**) and (*E*)-7-ethylheptadec-4-en-6-one (**31**).

Saturated Diketones. High-resolution GC-MS investigation of extract components revealed the presence of two oxygen atoms in 12 compounds. Their fragmentation is consistent with 2,4- or 4,6-alkanediones carrying an α-ethyl branch. The mass spectrum of 5-ethylnonane-2,4-dione (**33**) exhibited an acylium ion base peak at *m*/*z* 85 ($C_4H_5O_2^+$ by HR-MS) and a significant ion at *m*/*z* 128, formed by McLafferty rearrangement of the longer alkyl chain (Figure 1). A second acylium ion could be found at *m*/*z* 169. The bishomologue of **33**, 7-ethylundecane-4,6-dione (**38**), showed two acylium ions at *m*/*z* 113 and 169 as well as the McLafferty ions at *m*/*z* 156 and 184 in low abundance. Compounds **33** and **38** were synthesized by acylation of β-ketoesters with chlorides of 2-ethylalkanoic acids. Krapcho decarbethoxylation then furnished the desired diketones (Figure 3). Careful analysis of mass spectra and

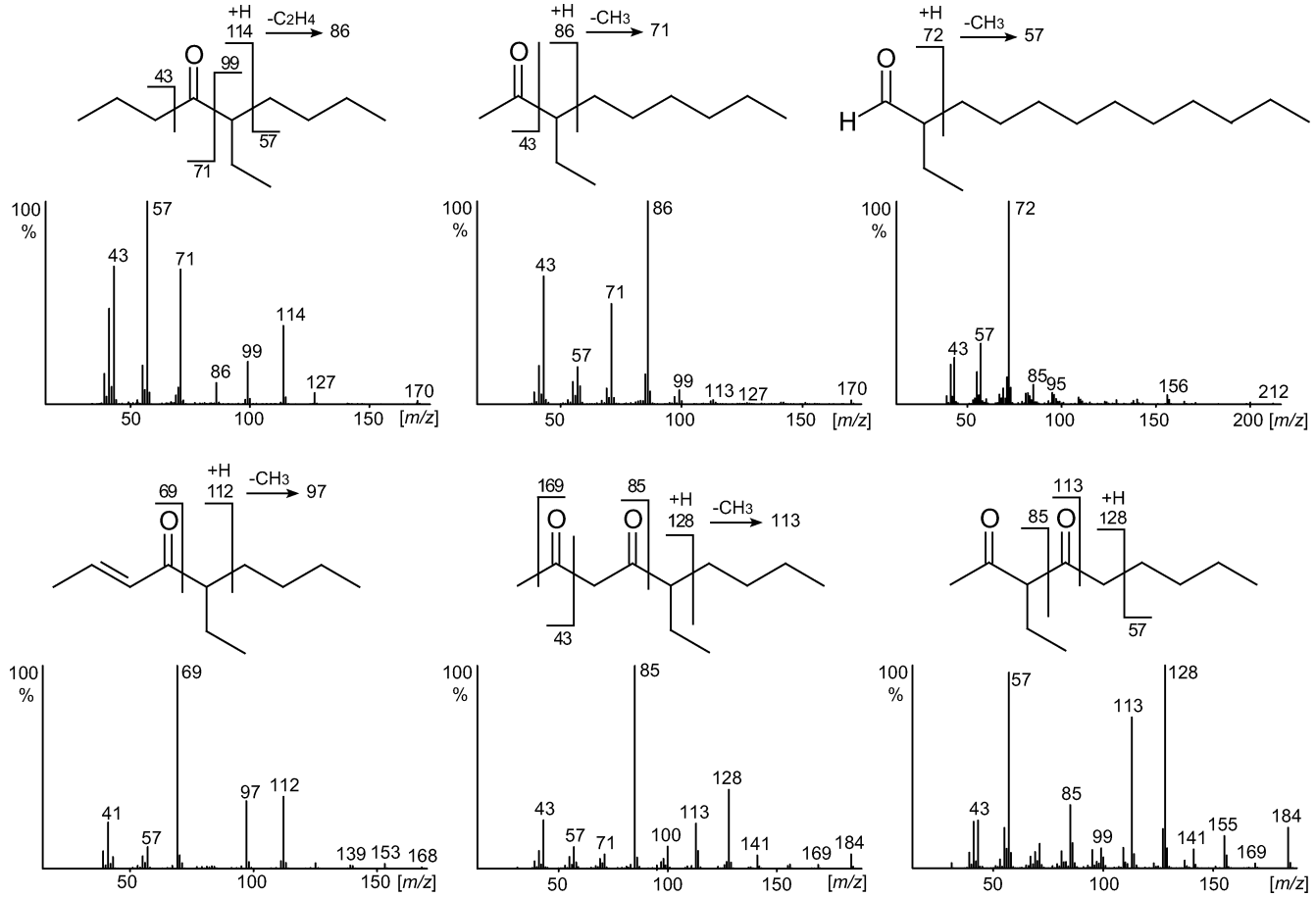


Figure 1. Mass spectrum and fragmentation patterns of 5-ethylnonan-4-one (**9**), 3-ethylnonan-2-one (**2**), 2-ethyldodecanal (**16**), (*E*)-5-ethylnon-2-en-4-one (**20**), 5-ethylnonane-2,4-dione (**33**), and 3-ethylnonane-2,4-dione (**42**).

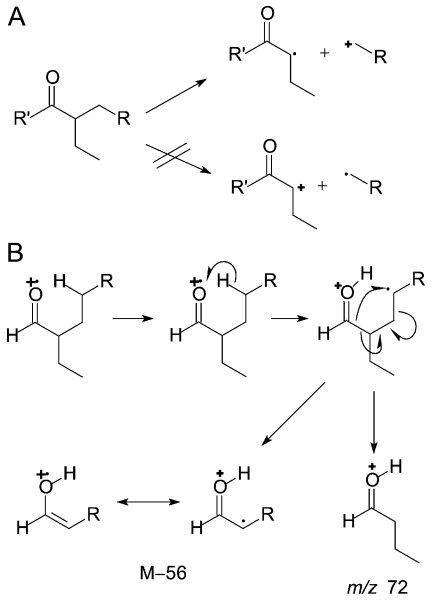


Figure 2. Characteristic mass spectrometric fragmentation of ethyl ketones (A) and ethyl aldehydes (B).

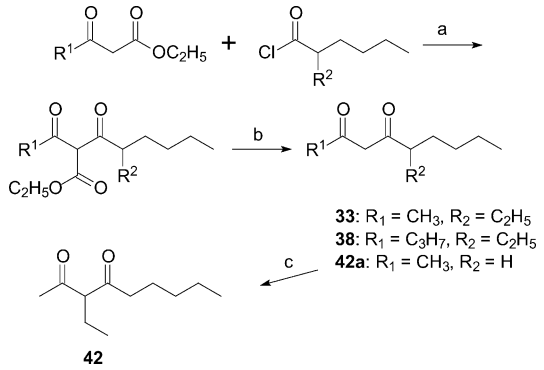


Figure 3. Synthesis of diketones **33**, **38**, and **42**: (a) $Mg(OEt)_2$; (b) NaCl, $DMSO/H_2O$; (c) NaOEt, EtI, DMF.

retention times confirmed the presence of a bishomologous series of both types of diketones ranging from C_9 to C_{15} (**33**−**40**). Furthermore, 5-ethylheptane-2,4-dione (**32**) and 7-ethylheptadecane-4,6-dione (**41**) were present. The only diketones not fitting this scheme were 3-ethylnonane-2,4-dione (**42**) and its bishomologue **43**, carrying the ethyl group between the two keto groups. The mass spectrum of **42** had a base peak at *m*/*z* 57. Ions at *m*/*z* 113 ($C_6H_9O_2^+$), accompanied by the respective McLafferty rearrangement ion at *m*/*z* 128 (Figure 1) and the acylium ion at *m*/*z* = 85, were characteristic. This compound was synthesized by reaction of ethyl acetoacetate with hexanoyl chloride, decarbethoxylation, and alkylation of the resulting diketone **42a** with ethyl iodide (Figure 3).

Configuration of the Ketones. To investigate the configuration of the ketones, we focused on a few compounds present in several species and in sufficient amounts. Therefore, we synthesized enantiomerically enriched samples of **9**, **12**, and **33** using Enders hydrazone technology. Undecan-6-one was converted into the SAMP hydrazone and then alkylated by treatment with LDA, followed by butyl iodide.[8] This procedure furnished *R*-**12** in good yield and an enantiomeric ratio of 85:15 (Figure 4). Similarly, reaction of the SAMP hydrazone of heptan-4-one and ethyl iodide led to *S*-**9** in an enantiomeric ratio of 82:12. It should be noted that the longer side chain was introduced in the first synthesis, while

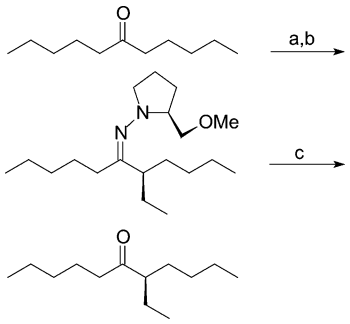


Figure 4. Synthesis of (*R*)-5-ethylundecan-6-one (*R*-**12**): (a) SAMP, toluene; (b) LDA, BuI, THF; (c) O_3.

the shorter one was introduced in the second. This explains the different configuration of the two products. The diketone *R*-**33** was synthesized starting from hexanal (Figure 5). Transformation into the SAMP-hydrazone followed by alkylation with ethyl iodide and ozonolysis afforded (*R*)-2-ethylhexanal. Oxidation to the acid by PDC/DMF and subsequent transformation into the acid chloride set the stage for the following acylation of ethyl acetoacetate. This conversion was done using magnesium chloride in pyridine. Final Krapcho decarbethoxylation furnished *R*-**33** in an enantiomeric ratio of 73:27. The incomplete stereoselectivity of these reactions was desired, because the mixtures allowed easy assignments of stereoisomers in the following investigations by chiral gas chromatography. Several chiral cyclodextrin phases were then tried to find optimal conditions for the resolution of the enantiomers by gas chromatography. The best results were obtained using a 2,6-di-*O*-methyl-3-*O*-pentyl-β-cyclodextrin (50% in OV 1701) phase, allowing separation of all three compounds in one run. The analysis of samples of all species containing the compounds showed that the *R*-enantiomers always were dominant. Small amounts of the *S*-enantiomers (up to 10%) also were detected, but it remains unclear whether these enantiomers are naturally present in the gland or are epimerization products. The known acidity of the α-hydrogens of a ketone points to the latter possibility. The results can be found in Table 2.

Bacteria of the Paracloacal Glands. The unusual ethyl branch in the chain of the ketones and aldehydes points to fatty acid- or polyketide-derived biosynthesis in which the normal malonate extender unit is modified by use of an ethylmalonate unit. Ethyl branches on malonate-derived chains are found with few exceptions[9] in natural products from microorganisms.[10] Staining of gland exudates of a male *C. crocodilus*, obtained from SA, with DAPI revealed high amounts of blue-colored particles that resembled bacteria in both size and shape. The particles appeared coccoid- or rod-shaped and were about 1−2 μm in size. The cultivation-independent approach, 16S rRNA gene library construction followed by RFLP analysis, produced two restriction patterns. Sequence analysis of clone K6 from one RFLP group showed the highest homology to a bacterial 16S rRNA gene sequence that was recovered from the teat canals of lactating bovines (AY676491, 92% sequence similarity). Strain *Luteococcus peritonei* (LSP132334) from the human peritoneum was the most closely related cultivated bacterium (Propionibacteriaceae, Actinobacteria, 92% sequence similarity over 1485 bp). Propionibacteria are rod-shaped, obligate anaerobes and commonly isolated from skin. Sequencing of clone K23 from the second RFLP group showed the highest homology to a group of taxonomically uncharacterized 16S rRNA gene sequences from contaminated groundwater (AF407407, 88% sequence similarity). Strain *Clostridium* sp. P6 (AY949857) was the most closely related cultivated isolate (Clostridiaceae, Firmicutes, 87% sequence similarity over 1472 bp). Clostridia are coccoid-shaped, endospore-forming, obligate anaerobes and commonly isolated from feces. The isolation of microorganisms on selective media produced nine morphologically distinguishable isolates that, upon partial sequencing of the 16S rRNA gene, fell into five taxonomic groups: *Paracoccus* (Alphaproteobacteria), *Corynebacterium* and *Arthrobacter* (Actinobacteria), and *Staphylococcus* and *Bacillus* (Firmicutes). Subsequent screening of the strains for the production of ketones and other gland constituents did not yield any of the compounds reported in this study.

Conclusion. In the *Caiman* species that we analyzed, a total of 40 ethyl-branched compounds were observed in adult females, 30 in adult males, and 12 in immature individuals (Table 1). In the *Paleosuchus* species, 11 compounds were observed in females, 11 in males, and 12 in immatures. Although some compounds were present in samples of only one sex, such as **14** in female *C. crocodilus* and *C. latirostris* and **28** in males of these species, we have not been able to make any judgment on possible sex differences in secretion composition, pending further investigations involving larger samples sizes.

Previous analyses of the paracloacal gland secretions of crocodylians have revealed, from among the more than 120 lipoidal compounds thus far identified from these organs,[2] no aldehydes and only two ketones, 11,12-dihydrocembren-10-one chiefly from adult male *Alligator sinensis* (Alligatoridae)[3,4] and dianeackerone from adult male and female *Osteolaemis tetraspis* (Crocodylidae).[5] 11,12-Dihydrocembren-10-one presumably arises from another glandular component, cembrene A. Cembrene A, which also occurs in many plants,[11] is formed by the cyclization of geranylgeranyl pyrophosphate.[12] Dianeackerone is an aromatic ethyl-branched ketone (C_{19}) thought to arise from the hydrolysis of sterols esterified with aromatic acids, which are abundant in the secretions of this species.[13]

The ethyl-branched aldehydes and ketones that we report here are not obviously related to other compounds known from *Caiman* or *Paleosuchus*, or of other alligatorids.[2] Neither have these compounds been reported from elsewhere in nature. Biosynthetically they are most probably formed via polyketide synthases using ethylmalonyl extender units instead of malonate.[10] Further studies on the biosynthesis of these unusual compounds are needed. Due to their structure and the fact that so far no polyketide synthase has been reported from animals, it is possible that microorganisms are involved in the formation of the ethyl ketones, even though a producing strain could not be isolated. The challenge of isolating

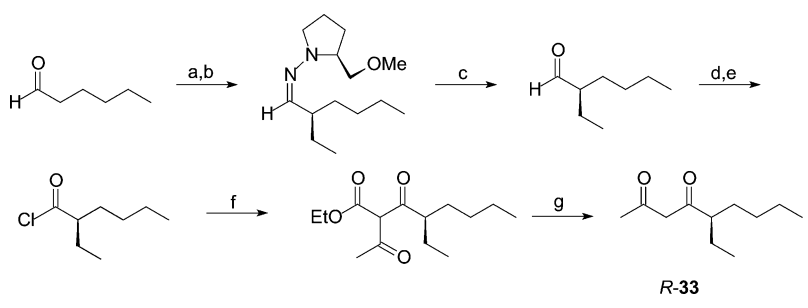


Figure 5. Synthesis of (*R*)-5-ethylnonane-2,4-dione (*R*-**33**): (a) SAMP, toluene; (b) LDA, EtI, THF; (c) O_3; (d) PDC, DMF; (e) $(COCl)_2$; (f) ethyl acetoacetate, $MgCl_2$, pyr; (g) NaCl, DMSO.

and identifying host-specific commensal and symbiotic microorganisms is commonly acknowledged.[14]

Experimental Section

General Experimental Procedures. The optical rotary power was measured using a Dr. Kernchen Propol digital automatic polarimeter. FT-IR spectra were obtained using a HP 6890 Series GC system connected to a HP 5965A infrared detector (Hewlett-Packard). ^{1}H NMR and ^{13}C NMR spectra were obtained with Bruker AC-200 and AMX-400 instruments. For NMR experiments, $CDCl_3$ was used; the internal standard was tetramethylsilane. GC-MS was carried out with a Hewlett-Packard model 5973 mass selective detector connected to a Hewlett-Packard model 6890 gas chromatograph. Analytical GLC analyses were carried out with a CE instruments GC 8000 gas chromatograph with a flame ionization detector and split/splitless injection. A 2,6-di-*O*-methyl-3-*O*-pentyl-β-cyclodextrin in 50% OV 1701 phase (15 m, 0.32 mm i.d.) was used for chiral GC. The gas chromatograph was programmed as follows: 5 min at 40 °C, then with 1 °C/min to 150 °C. All reactions were monitored by thin-layer chromatography (TLC) carried out on Macherey-Nagel Polygram SIL G/UV$_{254}$ silica plates visualized with heat gun treatment with 10% molybdatophosphoric acid in ethanol. Column chromatography was performed with Merck silica gel 60 (70−200 mesh). All reactions were carried out under an inert atmosphere of nitrogen in oven-dried glassware. Dry solvents: THF was distilled from sodium benzophenone, diethyl ether from $LiAlH_4$, and dichloromethane from CaH_2. All chemicals were commercially available (Fluka, Aldrich) and used without further treatment.

Animal Material. Paracloacal gland secretions of captive animals (total lengths in parentheses) were obtained from the Bronx Zoo, New York (BZ); the St. Augustine Alligator Farm, Florida (SA); Silver Springs Wildlife Park, Florida (SS); and the National Aquarium in Baltimore, Maryland (NA): one female *Alligator mississippiensis* (1.5 m) (SA); one male *A. sinensis* (1.2 m) (BZ); three females (0.25−0.45 m), three males (1.2−1.4 m) (SA and SS), and seven immatures (0.3 m) (SA) of *Caiman crocodilus*; one male (1.5 m) and five females (0.8−1.4 m) of *C. latirostris* (SA); two males (1.2 m) and five females (1.2−1.4 m) of *C. yacare* (SA and SS); one female *Melanosuchus niger* (1.5 m) (SA); two males (1.1−1.2 m), two females (1.1−1.2 m), and one immature (0.6 m) of *Paleosuchus palpebrosus* (BZ and SA); and two males (1.4−1.5 m), one female (1.4 m), and four immatures (0.5 m) of *P. trigonatus* (NA and SA). Samples were collected by manually palpating the glands and directing the secretions into glass vials containing several milliliters of pentane. Samples from some immatures were obtained in glass capillary tubes, which were broken off into glass vials containing pentane. Vials were placed on dry ice.

General Procedure for the Alkylation of Ketones. The ketones (1 equiv) were dissolved in dry THF and deprotonated with LiHMDS (1.1 equiv) or a previously prepared solution of LDA (1 equiv) at −30 °C. The reaction mixture was stirred for 30 min, and the alkyl halides were added. The quantity of alkyl halides and the reaction temperature varied due to the different reactivity. The reaction progress was monitored by TLC. Until complete consumption of the ketone the reaction mixture was diluted with Et_2O, water was added, and the phases were separated. Then the organic layer was washed with water and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica.

3-Ethylheptan-4-one (7). This compound was obtained from heptan-4-one (2.28 g, 20 mmol) and ethyl iodide (3.74 g, 24 mmol) as a colorless liquid (0.2 g, yield 7%) by heating the reaction mixture at reflux for 2 h: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.28−2.33 (2H, m, J = 7.3 Hz, 5.5 Hz, H-5), 2.21−2.26 (1H, m, J = 5.6 Hz, 8.0 Hz, H-3), 1.32−1.59 (8H, m, H-2, H-4a, H-5, H-6), 0.84 (6H, 2t, J = 7.4, 7.4 Hz, H-1, H-5a), 0.77 (3H, t, J = 7.5 Hz, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.7 (C, C-4), 55.4 (CH, C-3), 44.3 (CH_2, C-5), 24.3 (CH_2), 24.1 (CH_2), 16.9 (CH_2, C-6), 13.8 (CH_3), 13.6 (CH_3), 11.3 (CH_3); EIMS *m*/*z* 142 $[M]^+$ (15), 128 (2), 114 (5), 99 (12), 71 (100), 70 (10), 55 (10), 43 (52), 41 (14), 39 (7); HREIMS *m*/*z* 142.1357 (calcd for $C_9H_{18}O$, 142.1358).

5-Ethyloctan-4-one (8). This compound was obtained from heptan-4-one (0.57 g, 5 mmol) and propyl bromide (1.84 g, 15 mmol) as a colorless liquid (0.53 g, yield 68%) by heating the reaction mixture at reflux for 2 h: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.19−2.27 (3H, m, H-3, H-5), 1.04−1.49 (8H, m, H-2, H-6, H-6a, H-7), 0.67−0.77 (9H, m, H-1, H-7a, H-8); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.8 (C, C-4), 53.7 (CH, C-5), 44.8 (CH_2, C-3), 33.6 (CH_2), 24.7 (CH_2), 20.7 (CH_2), 16.9 (CH_2, C-2), 14.2 (CH_3), 13.8 (CH_3), 11.9 (CH_3); EIMS *m*/*z* 156 $[M]^+$ (2), 127 (3), 114 (36), 99 (9), 85 (77), 71 (76), 57 (16), 55 (19), 43 (100), 41 (42), 39 (17); HREIMS *m*/*z* 156.1483 (calcd for $C_{10}H_{20}O$, 156.1514).

5-Ethylnonan-4-one (9). This compound was obtained from heptan-4-one (0.228 g, 2 mmol) and butyl iodide (0.736 g, 4 mmol) as a colorless liquid (0.227 g, yield 67%) by stirring 3 h at room temperature: IR ν_{max} 2961, 2917, 1720, 1595 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.38 (2H, t, J = 7.3 Hz, H-3), 2.36 (1H, tt, J = 5.5 Hz, 8.0 Hz, H-5), 1.16−1.68 (10H, m, H-2, H-6, H-6a, H-7, H-8), 0.91 (3H, t, J = 7.4 Hz, H-1), 0.88 (3H, t, J = 7.3 Hz, H-7a), 0.85 (3H, t, J = 7.5 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.0 (C, C-4), 53.8 (CH, C-5), 44.2 (CH_2, C-3), 31.0 (CH_2), 29.7 (CH_2), 24.6 (CH_2), 22.8 (CH_2), 13.9 (CH_3), 13.8 (CH_3), 11.9 (CH_3); EIMS *m*/*z* 170 $[M]^+$ (5), 127 (7), 115 (4), 114 (49), 99 (29), 86 (12), 71 (85), 70 (8), 69 (10), 57 (100), 55 (13), 53 (5), 43 (67), 41 (37), 39 (17); HREIMS *m*/*z* 170.1682 (calcd for $C_{11}H_{22}O$, 170.1672).

5-Ethylundecan-4-one (10). This compound was obtained from heptan-4-one (0.228 g, 2 mmol) and hexyl iodide (0.848 g, 4 mmol) as a colorless liquid (0.21 g, yield 53%) by stirring the reaction mixture at room temperature for 16 h: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.31 (2H, t, J = 7.3 Hz, H-3), 2.21−2.26 (1H, m, H-5), 1.26−1.74 (14H, m, H-2, H-6, H-6a, H-7, H-8, H-9, H-10), 0.83−0.91 (9H, m, J = 7.2 Hz, 7.2 Hz, 7.5 Hz, H-1, H-7a, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 214.3 (C, C-4), 55.2 (CH, C-5), 44.1 (CH_2, C-3), 29.4 (CH_2), 27.5 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 22.1 (CH_2), 16.8 (CH_2, C-2), 13.9 (CH_3), 13.8 (CH_3), 11.9 (CH_3); EIMS *m*/*z* 198 $[M]^+$ (2), 169 (1), 155 (3), 141 (1), 127 (8), 114 (44), 99 (11), 86 (15), 85 (24), 71 (100), 70 (9), 57 (29), 55 (27), 43(92), 41 (71), 39 (18); HREIMS *m*/*z* 198.1971 (calcd for $C_{13}H_{26}O$, 198.1985).

5-Ethylundecan-6-one (12). This compound was obtained from undecan-6-one (0.85 g, 5 mmol) and ethyl iodide (1.54 g, 10 mmol) as a colorless liquid (0.415 g, yield 42%). The reaction mixture was heated to reflux for 2 h and then stirred for another 16 h: IR ν_{max} 2959, 2921, 1722, 1572, 1456 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.34−2.49 (3H, m, J = 7.4 Hz, 6.2 Hz, H-5, H-7), 1.14−1.69 (14H, m, H-2, H-3, H-4, H-6a, H-8, H-9, H-10), 0.82−0.91 (9H, m, J = 7.1 Hz, 7.5 Hz, 6.9 Hz, H-1, H-7a, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 215.1 (C, C-6), 53.9 (CH, C-5), 42.3 (CH_2, C-7), 31.56 (CH_2), 31.54 (CH_2), 29.7 (CH_2), 23.2 (CH_2), 22.9 (CH_2), 22.6 (CH_2), 22.5 (CH_2), 13.9 (CH_3, C-7a), 11.86 (CH_3), 11.82 (CH_3); EIMS *m*/*z* 198 $[M]^+$ (4), 169 (2), 155 (5), 142 (29), 127 (10), 100 (13), 99 (100), 98 (6), 86 (36), 71 (48), 57 (95), 55 (20), 43 (56), 41 (33), 39 (8); HREIMS *m*/*z* 198.1983 (calcd for $C_{13}H_{26}O$, 198.1985).

Preparation of 3-Ethylheptan-2-one (1). A suspension of 2-ethylhexanoyl chloride (0.325 g, 2 mmol) in 15 mL of $CHCl_3$ was cooled to 0 °C. Then *N*,*O*-dimethylhydroxylamine (0.22 g, 2.3 mmol) and pyridine (0.37 g, 4.4 mmol) were added, and the reaction mixture was stirred for 1 h. The solvent was evaporated under reduced pressure. The residue was partitioned between 30 mL of brine and 30 mL of a 1:1 mixture of Et_2O and CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$ and concentrated to yield the crude amide, which was purified by flash column chromatography (0.332 g, yield 89%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (3H, s, NOC*H*$_3$), 3.20 (3H, s, NC*H*$_3$), 1.21−1.65 (9H, m, H-2, H-3, H-3a, H-4, H-5), 0.88 (6H, 2t, J = 7.4, 7.1 Hz, C-4a, C-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 193.4 (C, C-1), 61.4 (CH, C-2), 53.4 (CH_3, NO*C*H$_3$), 42.2 (CH_3, N*C*H$_3$), 28.9 (CH_3, C-1), 32.2 (CH_2), 29.9 (CH_2), 25.7 (CH_2), 22.9 (CH_2), 14.1 (CH_3, C-4a), 12.1 (CH_3, C-6); EIMS *m*/*z* 187 $[M]^+$ (1), 172 (1), 127 (19), 116 (2), 99 (11), 57 (100), 55 (16), 43 (18), 41 (25). A solution of thus prepared *N*-methoxy-*N*-methyl-2-ethylhexanoylamide (0.187 g, 1 mmol) in 5 mL of dry THF was added to a previously prepared solution of methylmagnesium iodide (5 mmol) in THF. The reaction mixture was stirred at 0 °C until TLC showed complete consumption of the starting amide. The reaction was quenched with diluted HCl, and the mixture was partitioned between 20 mL of brine and 20 mL of a 1:1 mixture of Et_2O and CH_2Cl_2. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica, affording a colorless oil (0.089 g, yield 63%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ (3H, s, H-1), 2.11−2.23 (1H, m, H-3), 1.19−1.63 (8H, m, H-4, H-4a, H-5, H-6), 0.86 (3H, t, J = 7.5 Hz, H-5a), 0.79 (3H, t, J =

7.5 Hz, H-7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 211.3 (C, C-2), 55.2 (CH, C-3), 28.9 (CH_3, C-1), 27.4 (CH_2), 24.7 (CH_2), 21.2 (CH_2), 20.9 (CH_2), 13.6 (CH_3, C-5a), 11.9 (CH_3, C-7); EIMS *m*/*z* (%) 142 $[M]^+$ (4), 151 (1), 127 (1), 113 (4), 99 (11), 86 (100), 85 (22), 71 (47), 69 (9), 57 (29), 55 (13), 43 (62), 41 (26); HREIMS *m*/*z* 142.1349 (calcd for $C_9H_{18}O$, 142.1358).

Preparation of 5-Ethylnon-2-en-4-one (20). 20 was prepared from **9** (0.170 g, 1 mmol) by oxidation with iodosobenzoic acid according to the method of Nicolaou et al.[7] Compound **20** was obtained as a colorless oil (0.063 g, yield 38%): IR ν_{max} 3037, 2949, 2937, 2881, 1691, 1634, 1457, 1291 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (1H, dq, J = 15.6 Hz, 6.8 Hz, H-3), 6.21 (1H, dq, J = 15.6 Hz, 1.6 Hz, H-2), 2.58 (1H, tt, J = 5.5 Hz, 8.2 Hz, H-5), 1.90 (3H, dd, J = 1.6 Hz, 6.8 Hz, H-1), 1.15−1.66 (8H, m, H-6, H-6a, H-7, H-8), 0.87 (3H, t, J = 7.1 Hz, H-7a), 0.84 (3H, t, J = 7.3 Hz, H-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.0 (C, C-4), 142.0 (CH, C-3), 131.1 (CH, C-2), 51.1 (CH, C-5), 31.1 (CH_2), 29.5 (CH_2), 24.7 (CH_2, C-6a), 22.6 (CH_2, C-8), 18.1 (CH_3, C-1), 13.7 (CH_3), 11.7 (CH_3); EIMS *m*/*z* 168 $[M]^+$, 153 (2), 139 (1), 125 (3), 113 (3), 112 (30), 111 (3), 98 (3), 97 (31), 70 (6), 69 (100), 57 (12), 55 (7), 43 (7), 41 (28), 39 (12); HREIMS *m*/*z* 168.1479 (calcd for $C_{11}H_{20}O$, 168.1515).

Preparation of 5-Ethylundec-2-en-4-one (22). 22 was prepared from **10** (0.198 g, 1 mmol) by oxidation with iodosobenzoic acid according to the method of Nicolaou et al.[7] Compound **22** could only be obtained as an unseparable mixture with the starting material **10** (0.158 g, yield 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.92 (1H, dq, J = 15.2 Hz, 6.6 Hz, H-3), 6.24 (1H, m, J = 15.2 Hz, H-2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.4 (C, C-4), 144.1 (CH, C-3), 133.2 (CH, C-2); EIMS *m*/*z* 196 $[M]^+$ (2), 181 (3), 167 (2), 153 (2), 181 (2), 112 (27), 97 (18), 69 (100), 55 (14), 41 (55); HREIMS *m*/*z* 196.1842 (calcd for $C_{13}H_{24}O$, 196.1827).

(*E*)-7-Ethylundec-4-en-6-one (27). Dry aluminum chloride (2.67 g, 20 mmol) was added to a solution of 2-ethylhexanoyl chloride (3.25 g, 20 mmol) in dry CH_2Cl_2 (17 mL) in portions at 0 °C and stirred until all solid was dissolved. Then 1-pentene (2.81 g, 40 mmol) was added dropwise at the same temperature.[15] After stirring at room temperature for 24 h, the mixture was poured onto an ice−diethyl ether mixture, the ether layer was separated, and the aqueous layer was repeatedly extracted with ether. The combined ether extracts were washed with 15% potassium carbonate solution and with water and dried with $MgSO_4$. The solvent was removed and the residue was purified by flash chromatography (SiO_2, 2.5% diethyl ether in pentane). Pure **27** was isolated as a colorless oil (0.43 g, yield 11%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 (1H, dt, J = 15.7, 7.0 Hz, H-4), 6.18 (1H, dt, J = 15.7, 1.5 Hz, H-5), 2.60 (1H, m, H-7), 2.20 (2H, m, H-3), 1.46 (10H, m, H-2, H-8, H-9, H-10, H-1′), 0.94 (3H, t, J = 7.4 Hz, C*H*$_3$), 0.86 (6H, m, 2 × C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.2 (C, C-6), 146.9 (CH, C-4), 129.9 (CH, C-5), 51.2 (CH, C-7), 34.4 (CH_2, C-3), 31.3 (CH_2), 29.7 (CH_2), 25.0 (CH_2), 22.8 (CH_2), 21.4 (CH_2), 13.9 (CH_3), 13.6 (CH_3), 11.8 (CH_3); HREIMS *m*/*z* 196.1851 (calcd for $C_{13}H_{24}O$, 196.1827).

2-Ethyldodecanal (16). Methyl dodecanoate was alkylated with ethyl iodide using a modified published procedure.[16,17] Thus, diisopropylamine (3.04 g, 30 mmol) in dry THF (12 mL) was added dropwise to a solution of *n*-butyllithium in hexane (1.6 M, 12.5 mL, 20 mmol). After stirring for 10 min all solvents and volatile compounds were evaporated in vacuo and the residue was dissolved in dry THF (20 mL). The resulting 1 M LDA solution was cooled to −78 °C. At this temperature, methyl dodecanoate (4.29 g, 20 mmol) was added slowly and the mixture was stirred for 20 min. Then a solution of ethyl iodide (3.43 g, 22 mmol) in DMPU (0.73 mL) was added. The mixture was allowed to warm to −40 °C and then quenched with saturated NH_4Cl solution. The mixture was acidified with 2 N HCl and extracted repeatedly with ether. The combined ether extracts were washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. Thus, methyl 2-ethyldodecanoate (4.61 g, yield 95%) was obtained as a colorless oil. Reduction with $LiAlH_4$ according to known procedures furnished 2-ethyldodecan-1-ol (yield 90%). 2-Ethyldodecanal was finally obtained by oxidation with PDC in CH_2Cl_2 (yield 55%).[18] This compound is rapidly oxidized to the corresponding acid in air: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.57 (1H, d, J = 3.0 Hz, H-1), 2.17 (1H, m, H-2), 1.55 (4H, m, H-3, H-1′), 1.26 (16H, br s, H-4, H-5, H-6, H-7, H-8, H-9, H-10, H-11), 0.91 (3H, t, J = 7.5 Hz, C*H*$_3$), 0.88 (3H, t, J = 6.3 Hz, C*H*$_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.7 (CH, C-1), 53.4 (CH, C-2), 31.9 (CH_2), 29.7 (CH_2), 29.58 (CH_2), 29.56 (CH_2), 29.4 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.1 (CH_2), 22.7 (CH_2), 21.9 (CH_2), 14.1 (CH_3), 11.4 (CH_3); HREIMS *m*/*z* of the respective 2,4-dinitrophenylhydrazone 392.2420 (calcd for $C_{20}H_{32}N_4O_4$, 392.2418).

General Procedure for the Synthesis of Diketones. The β-keto ester (1 equiv) was dissolved in a 4:1 mixture of Et_2O and EtOH and added to a previously prepared solution of magnesium ethanolate (1 equiv). Then the respective acid chloride (1 equiv) was added carefully, and the reaction mixture was stirred for 16 h. The reaction was quenched with ice and diluted H_2SO_4, and the phases were separated. The aqueous layer was extracted with Et_2O three times, and the combined organic phases were washed with water. After drying ($MgSO_4$) and removal of the solvent, the crude product was used in the Krapcho decarbethoxylation.[19] The crude product was dissolved in a suspension of aqueous DMSO and sodium chloride. The reaction mixture was heated to reflux for 12 h. After cooling to room temperature the mixture was diluted with water and extracted twice with EtO_2. The organic layer was washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the crude product was purified by flash column chromatography on silica.

5-Ethylnonane-2,4-dione (33). This compound was obtained from ethyl acetoacetate (1.3 g, 10 mmol) and 2-ethylhexanoyl chloride (1.62 g, 10 mmol) as a brownish liquid (1.14 g, yield 62%): IR ν_{max} 2984, 2942, 2882, 1714, 1609, 1459, 1352 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 15.5 (br s, OH), 5.48 (s, H-3), 3.58 (s, H-3), 2.36 (tt, J = 8.1 Hz, 5.6 Hz, H-5), 2.24 (tt, J = 5.8 Hz, 8.4 Hz, H-5), 2.11 (3H, s, H-1), 1.19−1.65 (8H, m, H-6, H-6a, H-7, H-8), 0.84−0.91 (6H, m, H-7a, C-9); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 213.1 (C, C-4), 196.7 (C, C-4), 192.2 (C, C-2), 176.5 (C, C-2), 99.9 (CH, C-3), 59.7 (CH_2, C-3), 49.8 (CH, C-5), 47.1 (CH, C-5), 28.5 (CH_3, C-1), 25.1 (CH_3, C-1), 25.4 (CH_2), 24.2 (CH_2), 23.2 (CH_2), 22.1 (CH_2), 13.8 (CH_3), 13.7 (CH_3), 11.7 (CH_3), 11.6 (CH_3); EIMS *m*/*z* 184 $[M]^+$ (3), 169 (1), 155 (1), 141 (3), 128 (29), 114 (7), 113 (8), 100 (10), 86 (5), 85 (100), 71 (6), 70 (5), 57 (15), 55 (9), 43 (39), 41 (16); HREIMS *m*/*z* 184.1449 (calcd for $C_{11}H_{20}O_2$, 184.1464).

7-Ethylundecane-4,6-dione (38). This compound was obtained from ethyl 3-oxohexanoate (1.58 g, 10 mmol) and 2-ethylhexanoyl chloride (1.62 g, 10 mmol) as a light brown liquid (0.32 g, yield 15%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.46 (s, H-5), 3.55 (s, H-5), 2.27 (2H, t, J = 7.3 Hz, H-3), 2.03−2.09 (1H, m, H-7), 1.68−2.00 (10H, m, H-2, H-8, H-8a, H-9, H-10), 0.96 (3H, t, J = 7.4 Hz, H-9a), 0.85−0.92 (6H, m, H-1, H-11); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.1 (C, C-4), 194.8 (C, C-6), 99.5 (CH_2, C-5), 50.2 (CH, C-7), 40.5 (CH_2, C-3), 32.2 (CH_2, C-9), 29.7 (CH_2, C-8), 25.9 (CH_2, C-10), 22.8 (CH_2, C-8a), 19.2 (CH_2, C-2), 13.9 (CH_3), 13.7 (CH_3), 11.9 (CH_3, C-9a); EIMS *m*/*z* 212 $[M]^+$ (3), 169 (11), 156 (24), 142 (6), 128 (6), 113 (100), 97 (9), 71 (31), 57 (24), 43 (29); HREIMS *m*/*z* 212.1771 (calcd for $C_{13}H_{24}O_2$, 212.1776).

Preparation of 3-Ethylnonane-2,4-dione (42). Nonane-2,4-dione was obtained from ethyl acetoacetate (1.3 g, 10 mmol) and hexanoyl chloride (1.34 g, 10 mmol) as a light brown liquid (1.14 g, yield 62%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 15.6 (br s, OH), 5.48 (s, H-3), 3.61 (s, H-3), 2.35 (tt, J = 8.1 Hz, 5.7 Hz, H-5), 2.26 (tt, J = 5.9 Hz, 8.3 Hz, H-5), 2.12 (1H, s, H-1), 1.19−1.65 (6H, m, H-6, H-7, H-8), 0.89 (3H, t, H-9); ^{13}C NMR (100 MHz) δ 193.4 (C, C-4), 191.5 (C, C-2), 99.7 (CH_2, C-3), 57.9 (CH_2, C-3), 38.2 (CH_2, C-5), 31.4 (CH, C-1), 25.4 (CH_2), 25.0 (CH_2), 22.4 (CH_2, C-8), 13.8 (CH_3, C-9); EIMS *m*/*z* 156 $[M]^+$ (5), 141 (8), 114 (11), 113 (23), 100 (52), 86 (4), 85 (100), 71 (6), 70 (5), 57 (11), 55 (13), 43 (64), 41 (21). A solution of nonane-2,4-dione (0.78 g, 5 mmol) in THF was treated with potassium carbonate (0.69 g, 5 mmol). After being stirred for 1.5 h at room temperature, ethyl iodide (1.56 g, 10 mmol) was added. The reaction mixture was stirred for another 16 h and then quenched with water. The aqueous layer was extracted three times with EtO_2. After washing the combined ether phases with water and drying over $MgSO_4$, the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography on silica (0.386 g, yield 42%): IR ν_{max} 2967, 2923, 2887, 1717, 1609, 1458 cm^{-1}; ^{1}H NMR (400 MHz) δ 3.44 (1H, t, J = 7.5 Hz, H-3), 2.39 (2H, t, J = 7.2 Hz, H-5), 2.23 (3H, s, H-1), 1.19−1.82 (8H, m, H-4a, H-6, H-7, H-8), 0.93 (3H, t, J = 7.2 Hz, H-5a), 0.89 (3H, t, J = 7.4 Hz, H-9); ^{13}C NMR (100 MHz) δ 204.5 (C, C-4), 199.7 (C, C-2), 67.2 (CH, C-3), 38.2 (CH_2, C-5), 30.3 (CH_3, C-1), 25.4 (CH_2), 25.2 (CH_2), 22.4 (CH_2), 21.3 (CH_2), 13.8 (CH_3, C-9), 11.9 (CH_3, C-5a); 184 $[M^+]$ (22), 155 (18), 141 (13), 128 (100), 127 (24), 113 (72), 109 (13), 99 (15), 85 (21), 57

(91), 55 (22), 43 (27), 41 (31); HREIMS *m/z* 184.1458 (calcd for $C_{11}H_{20}O_2$, 184.1464).

General Procedure for the Enantioselective Alkylation of Ketones. The alkylation was performed by a procedure according to Enders et al.[8] SAMP (1 equiv) is added to a solution of the carbonyl compound (1 equiv) in dry benzene. The mixture was heated at reflux for 3 h, diluted with Et_2O, washed with saturated aqueous $NaHCO_3$ twice, and dried over $MgSO_4$. Removal of the solvent furnished the crude hydrazone.

The hydrazone (1 equiv) was dissolved in dry THF and added to a previously prepared solution of LDA (1.05 equiv) at −78 °C. After stirring for 1 h, the reaction mixture was cooled to −110 °C. The alkyl halide was added, and after another 2 h of stirring at −110 °C the reaction mixture was warmed to room temperature during a period of 4 h. The mixture was diluted with Et_2O and washed with water twice. The aqueous layer was extracted with EtO_2, and the combined ether extracts were dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and crude alkylated hydrazone was obtained.

The hydrazone was dissolved in CH_2Cl_2 and cooled to −78 °C for cleavage by ozonolysis. A constant stream of ozone was flushed through the solution until the color of the solution turned blue. Nitrogen was flushed through the mixture as it warmed to room temperature. The mixture was concentrated under reduced pressure, and the crude product was purified by flash column chromatography on silica.

Preparation of (*S*)-5-Ethylnonan-4-one (*S*-9). Heptan-4-one (0.23 g, 2 mmol) and SAMP (0.26 g, 2 mmol) furnished (*S*)-methoxymethyl-1-(1-propylbutylidenamino)pyrrolidine, which was alkylated with butyl iodide (0.22 g, 1.2 mmol). The resulting (*S*)-methoxymethyl-1-(2-ethyl-1-propylhexylidenamino)pyrrolidine (0.206 g, 0.73 mmol) gave after ozonolysis (*S*)-**9** as a colorless liquid (0.12 g, yield 95%): $[\alpha]^{20}_D$ +161; ee = 63.4% (GC).

Preparation of (*R*)-5-Ethylundecan-6-one (*R*-12). Undecan-6-one (0.34 g, 2 mmol) and SAMP (0.26 g, 2 mmol) furnished methoxymethyl-1-(1-pentylhexylidenamino)pyrrolidine (0.49 g, 1.8 mmol), which was alkylated with ethyl iodide (0.8 g, 5.6 mmol). The resulting (*S*)-methoxymethyl-1-(2-ethyl-1-pentylhexylidenamino)pyrrolidine (0.497 g, yield 88%) gave after ozonolysis (*R*)-**12** as a colorless liquid (0.15 g, yield 78%): $[\alpha]^{20}_D$ −48; ee = 70.8% (GC).

Synthesis of (*R*)-5-Ethylnonane-2,4-dione (*R*-33). (*R*)-2-Ethylhexanal was prepared from hexanal and SAMP as described above. The resulting methoxymethyl-1-(hexylidenamino)pyrrolidine was alkylated with ethyl iodide, followed by ozonolysis in 90% overall yield. NMR and MS data matched published data.[20,21] This aldehyde (1.26 g, 9.8 mmol) was converted into (*R*)-2-ethylhexanoic acid in 48% yield by reaction of PDC (4.14 g, 11 mmol) and 15 mL of dry DMF according to the Corey−Schmidt procedure.[18] NMR data matched published data.[18] The corresponding acid chloride was obtained by addition of oxalyl chloride (1.27 g, 10 mmol) to a solution of the acid (0.586 g, 4.07 mmol) in dry toluene. The reaction mixture was heated to reflux for 2 h, and the toluene and the remaining oxalyl chloride were removed under reduced pressure. The product was obtained as a light brown liquid (0.276 g, yield 42%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (1H, tt, J = 5.4 Hz, 8.3 Hz, H-2), 1.55−1.83 (4H, m, H-3, H-3a), 1.26−1.39 (4H, m, H-4, H-5), 0.96 (3H, t, J = 7.4 Hz, H-4a), 0.91 (3H, t, J = 7.0 Hz, H-6); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.0 (C, C-1), 58.8 (CH, C-2), 31.3 (CH_2), 29.1 (CH_2), 25.1 (CH_2), 22.5 (CH_2), 13.8 (CH_3, C-4a), 11.3 (CH_3, C-6); EIMS *m/z* $[M]^+$ − Cl (4), 108 (7), 106 (22), 99 (11), 98 (4), 91 (6), 83 (2), 71 (5), 70 (15), 69 (5), 57 (100), 56 (7), 55 (25), 43 (26), 41 (40), 39 (15). In the final step ethyl acetoacetate (0.222 g, 1.7 mmol) was added to a suspension of anhydrous $MgCl_2$ (0.162 g, 1.7 mmol) in 10 mL of dry CH_2Cl_2. The reaction mixture was cooled to 0 °C, and pyridine was added (0.27 g, 3.4 mmol). After stirring for 15 min, (*R*)-2-ethylhexanoyl chloride (0.276 g, 1.7 mmol) was added slowly. The reaction mixture was stirred for 1 h at 0 °C and another 16 h at room temperature. Then the reaction was quenched with diluted HCl. After extraction with Et_2O, the combined organic phases were dried with $MgSO_4$. Removal of the solvent furnished the crude product, which was employed in the Krapcho decarbethoxylation as described previously. ***R*-33** was obtained as a dark brown liquid (0.31 g, yield 99%): $[\alpha]^{20}_D$ −1.2; ee = 46.4% (GC).

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Supporting Information Available: Table of MS data and retention indices of compounds **1**−**43** and description of microbiological methods. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Weldon, P. J.; Ferguson, M. W. J. *Brain Behav. Evol.* **1993**, *41*, 239−245.
(2) Weldon, P. J.; Wheeler, J. W. In *Crocodilian Biology and Evolution*; Grigg, G. C., Seebacher, F., Franklin, C. E., Eds.; Surrey Beatty & Sons: Chipping Norton, New South Wales, Australia, 2000; pp 286−296.
(3) Mattern, D. L.; Scott, W. D.; McDaniel, C. A.; Weldon, P. J.; Graves, D. E. *J. Nat. Prod.* **1997**, *60*, 828−831.
(4) Schulz, S.; Krückert, K.; Weldon, P. J. *J. Nat. Prod.* **2003**, *66*, 34−38.
(5) Whyte, A.; Yang, Z.-C.; Tiyanont, K.; Weldon, P. J.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 12246−12250.
(6) *Wiley Registry of Mass Spectral Data*, 7th ed.; John Wiley & Sons: New York, 2000.
(7) Nicolaou, K. C.; Montagnon, T.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2245−2258.
(8) Enders, D.; Eichenauer, H. *Chem. Ber.* **1979**, *112*, 291−296.
(9) Bartelt, R. J.; Weisleder, D. *Bioorg. Med. Chem.* **1996**, *4*, 429−438.
(10) O'Hagan, D. *The Polyketide Metabolites*; Ellis Horwood: Chichester, UK, 1991.
(11) Connolly, J. D.; Hill, R. A. *Dictionary of Terpenoids*; Chapman & Hall: London, 1991; Vol. 2.
(12) MacMillan, J.; Beale, M. In *Comprehensive Natural Products Chemistry*; Barton, D., Nakanishi, K., Meth-Cohn, O., Cane, D. E., Eds.; Elsevier: Amsterdam, 1999; Vol. 2, pp 217−243.
(13) Yang, Z.; Whyte, A.; Attygalle, A. B.; Weldon, P. J.; Eisner, T.; Meinwald, J. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 12251−12256.
(14) Piel, J. *Nat. Prod. Rep.* **2004**, *21*, 519−538.
(15) Melikyan, G. G.; Atanesyan, K. A.; Simonyan, S. O.; Badanyan, S. O. *J. Org. Chem. USSR* **1983**, *19*, 1032−1035.
(16) Herrmann, J. L.; Schlessinger, R. H. *J. Chem. Soc., Chem. Commun.* **1973**, 711−712.
(17) Cregee, R. J.; Herrmann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *26*, 2425−2428.
(18) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399−402.
(19) Krapcho, A. P. *Synthesis* **1982**, 893−914.
(20) Hodgson, D. M.; Bray, C. D.; Kindon, N. D. *J. Am. Chem. Soc.* **2004**, *126*, 6870−6871.
(21) Gilpin, J. A.; McLafferty, F. W. *Anal. Chem.* **1957**, *29*, 990−992.

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