Polycyclic Polyprenylated Acylphloroglucinols

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Contents

1. Introduction

In recent years, the antidepressant activity of *Hypericum perforatum*, commonly known as St. John's wort, has attracted much attention from both scientists[1–4] and the wider public.[5] Investigations of the constituents of St. John's wort and other plants from the family Guttiferae and related families have revealed a class of compounds, polycyclic polyprenylated acylphloroglucinols (PPAPs), with fascinating chemical structures and intriguing biological activities. The PPAPs feature a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,9-trione or bicyclo[3.2.1]octane-2,4,8-trione core decorated with C_5H_9 or $C_{10}H_{17}$ (prenyl, geranyl, etc.) side chains (the latter in several isomeric forms). The PPAPs can be divided into three classes: type A PPAPs have a C(1) acyl group and an adjacent C(8) quaternary center, type B PPAPs have a C(3) acyl group, and the rare type C PPAPs have a C(1) acyl group and a distant C(6) quaternary center (Figure 1).[6] Secondary cyclizations involving the β-diketone and pendant olefinic groups may occur to afford adamantanes, homoadamantanes, pyrano-fused, or other cyclized structures.

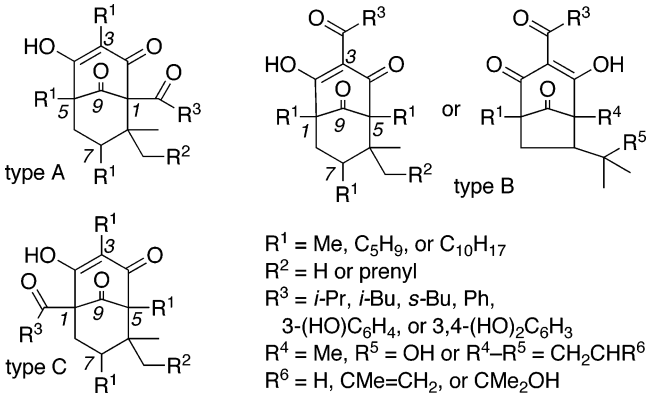

Figure 1. Type A, B, and C PPAPs.

PPAPs are biosynthetically derived from the less complex monocyclic polyprenylated acylphloroglucinols (MPAPs), which are found in many plants from the Myrtaceae and Cannabinaceae families, often as dimers. MPAPs are reported to show antimicrobial, antifungal, and antifeedant activity.[7] For example, *Humulus lupulus* (Cannabinaceae), commonly known as hops, is used in folk medicine as an antibacterial (in the form of wound powders and salves), a tranquilizer (sleep inducer), and a diuretic and to ameliorate the symptoms of menopause. Perhaps more importantly, the female inflorescences (hop cones) of hops are also used in beer production. Two classes of MPAPs are found in hops (Figure 2). The α-acids are converted during the brewing process into iso-α-acids, the compounds that are responsible for the flavor and bitter taste of beer.[8] The β-acids do not add any taste because of decomposition. Although β-acids

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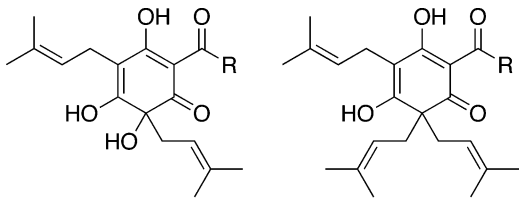
Robert B. Grossman, a native of Long Island, NY, earned his A.B. at Princeton University, where he carried out research under the direction of Robert A. Pascal. After graduating in 1987, he moved to MIT and worked under the direction of Stephen L. Buchwald to develop zirconium- and titanium-mediated and -catalyzed organic synthetic methodology. He earned his Ph.D. in 1992 and moved from Steve's lab in Cambridge, MA, to Steve's lab in Cambridge, England, where he worked in the Ley group on various aspects of the chemistry of azadirachtin. In 1994 he left the U.K. to join the faculty at UK in Lexington, KY. His research interests are currently focused on synthetic methodology, total synthesis, and biosynthetic pathways. He is the author of *The Art of Writing Reasonable Organic Reaction Mechanisms*, 2nd ed. (Springer, 2002), and one of the cocreators of ACE Organic, a Web-based organic chemistry homework program that provides response-specific feedback to structures drawn by students.

are not important to the brewing industry, they show radical scavenging activity, inhibition of lipid peroxidation, and antimicrobial activity.[2]

Little is known about the chemical synthesis of these hop acids, most of the studies dating from the early 1970s.[9] Several β-acids and analogues were prepared in very low to moderate yield; no α-acids were prepared.

2. Survey of PPAPs

All type A, B, and C PPAPs reported (to our knowledge) by the end of 2005 are presented in Tables 1−3, respectively.



R	α-acids	β-acids
i-Pr	cohumulone	colupulone
i-Bu	humulone	lupulone
s-Bu	adhumulone	adlupulone

Figure 2. Hops-derived α- and β-acids.

All have been isolated from plants in the family Guttiferae. In the course of collating the material for this review, we have had occasion to question whether certain PPAPs' structures have been correctly assigned. We discuss in the next two sections how we have decided whether to retain or correct the structures of various PPAPs in this review.

2.1. Reassignment of Certain PPAPs' Skeletons

The first scientists to isolate nemorosone and hydroxynemorosone assigned them type C structures.[10,11] Cuesta-Rubio later showed that nemorosone in fact had the type A structure **5**, in which the positions of the bridgehead substituents were swapped from their originally assigned positions.[6] Cuesta-Rubio did not revisit the structure of hydroxynemorosone, but, given its coisolation with **5** and the paucity of type C PPAPs, we venture to suggest that hydroxynemorosone also has a type A structure, namely, **6**.

Currently, only three PPAPs, garcinielliptones K−M (**117**−**119**), are reported to have type C structures.[12] It is reasonable to ask whether the structures of garcinielliptones K−M have been incorrectly determined. After all, the biosynthesis of type C PPAPs cannot occur from the intermediate common to type A and B PPAPs (vide infra). Moreover, if the two bridgehead groups of garcinielliptone K, L, and M are switched, the structures become identical to those of hyperibone B,[13] garsubellin C, and garsubellin D (**29**, **32**, and **27**),[14,15] respectively, and the garsubellins and garcinielliptones are both isolated from *Garcinia subelliptica*.[12,14,15] However, the type C structures of at least garcinielliptones K and M seem secure due to the observation of an NOE interaction between an ortho H atom of the benzoyl group and one of the H(8) atoms in these two compounds.[12] Also, the NMR spectra of garcinielliptone K and hyperibone B in $CDCl_3$ differ, so it is unlikely that the structure of garcinielliptone K has been misassigned and that the two compounds are both **29**.[12,13] Unfortunately, the NMR spectra of the garsubellins were measured in C_6D_6,[14,15] and those of the garcinielliptones were measured in $CDCl_3$,[12] so the spectra of garcinielliptones L and M cannot simply be compared to those of garsubellins C and D to determine whether they are identical. In conclusion, at this time, the structures assigned to garcinielliptones K−M appear to be secure, notwithstanding their unique type C skeletons.

Hyperibone K (**116**) is unusual in that it is the only example to date of a type B PPAP that has cyclized further to an adamantane or homoadamantane,[16] although there are many examples of type A PPAPs that have done so. However, the type B structure of **116** appears to be secure by virtue of HMBC correlations.

2.2. Reassignment of Certain PPAPs' Relative Stereochemistry

The structure of garcinielliptone I (**34**) has been reported to be identical to that of hyperibone B (**29**), but careful comparison of the NMR spectra and optical rotations induces us to propose instead that **34** is enantiomeric to hyperibone A (**33**).[13,17]

Grossman and Jacobs have shown that the orientation of the C(7) substituent in PPAPs (endo or exo) is easily determined by examining the ^{1}H and ^{13}C NMR spectra of the PPAPs.[18] When the C(7) substituent is exo, the difference in chemical shifts of the two H(6) atoms is 0.3−1.2 ppm, and the chemical shift of C(7) is 41−44 ppm, but when the C(7) substituent is endo, either the difference in chemical shifts of the two H(8) atoms is 0.0−0.2 ppm or the chemical shift of C(7) is 45−49 ppm. A compilation of the NMR data reported for all PPAPs in this review that have carbon skeletons of the bicyclo[3.3.1]nonane type (Figure 3) reveals that this correlation holds very consistently, regardless of NMR solvent, PPAP type, or nature of the C(7) substituent, and only a few exceptions to the correlation are found. These exceptions are discussed next.

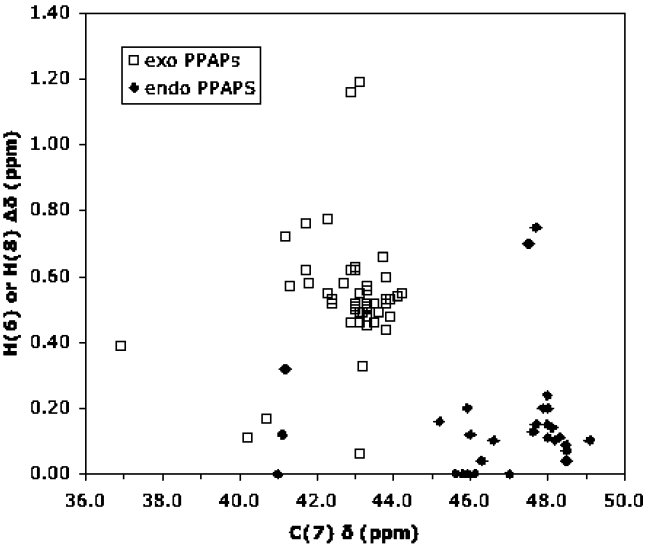


Figure 3. Correlation of C(7) configurations of PPAPs with bicyclo[3.3.1]nonane carbon skeletons with their C(7) δ values and H(6) or H(8) $\Delta\delta$ values. Hyperibones C, E, F, H, and I and hypersampsone F are included among the endo PPAPs (see text).

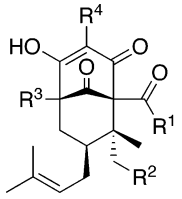
Hyperibones C, E, F, H, and I and hypersampsone F (**35**, **20**, **21**, **101**, **102**, and **42**, respectively) are all reported to have C(7) exo substituents, but neither their C(7) δ values (45.6−48.5 ppm) nor their H(6) or H(8) $\Delta\delta$ values (up to 0.11 ppm) are consistent with those of other exo PPAPs.[13,19] The paper describing hyperibones A−I does not report any data in support of the exo assignments for hyperibones C, E, F, H, and I, although it does report NOE data in support of exo assignments for hyperibones A, B, and D.[13] Furthermore, in hyperibone H (**101**), the only one of these compounds in which the two H(6) or H(8) atoms have anisochronous resonances, the H(7)−H(8)$_{ax}$ coupling constant is only 7.5 Hz, a value that favors an assignment of an endo configuration to C(7).[20] Similarly, no experiments to support the original exo assignment of hypersampsone F are reported.[19] As a result, we propose that hyperibones C, E, F, H, and I and hypersampsone F have endo C(7) substituents, not exo as originally proposed. We also propose that the C(6) prenylmethyl group of hypersampsone F is exo and trans to the C(7) prenyl group, as observed in C(7) endo PPAPs guttiferones A, C, and D[21] and as expected from the postulated mechanism of cyclization of MPAPs to PPAPs (anti addition across a geranyl group with retention of the geranyl group's configuration; vide infra).[6]

The guttiferone I reported by Herath et al. (two compounds have been called by this name) is reported to have a C(7) endo substituent,[22] but neither its C(7) δ value (41.2 ppm) nor its H(8) $\Delta\delta$ value (0.72 ppm) nor its H(7)−H(8)$_{ax}$ coupling constant (13.0 Hz) is consistent with those of other endo PPAPs. Herath's guttiferone I is isolated from the same species as guttiferone G, **97**,[23] and the NMR spectra of the two compounds are "similar".[22] Herath et al. conclude that their guttiferone I is different from **97** because of its quite different optical rotation (+8.7° for **98** vs −25° for **97**), but optical rotations are notoriously sensitive to the presence of impurities. Furthermore, they explain the H(7)−H(8)$_{ax}$ coupling constant of 13.0 Hz in their guttiferone I as being due to a flattened boat conformation of the ring containing C(6−8), but the fact that no other endo PPAP shows an H(7)−H(8)$_{ax}$ coupling constant greater than about 7.5 Hz casts serious doubt upon this rationalization.[20] Finally, they report NOESY data for their guttiferone I that are consistent with the endo isomer, but the data are equally consistent with the exo isomer. For these reasons, it must be concluded that Herath's guttiferone I is really identical to guttiferone G and that one or the other optical rotation reported for this compound is inaccurate. The name "guttiferone I" can now be reserved for Nilar's isolate, **87**.[24]

A handful of other PPAPS are also reported to have C(7) δ or H(6) or H(8) $\Delta\delta$ values that are inconsistent with those of other PPAPs of the same configuration. Endo PPAPs **98** (isogarcinol), **99** (isoxanthochymol, *ent*-**98**), and **25** are reported to have H(6) or H(8) $\Delta\delta$ values characteristic of exo compounds (0.75 and 0.70 ppm, respectively),[21,25] and exo PPAPs **30** and **94** (garcinielliptone FB and aristophenone) are reported to have H(6) or H(8) $\Delta\delta$ values characteristic of endo compounds (0.06 and 0.11−0.17 ppm, depending on the tautomer, respectively),[20,26] although the C(7) δ values of all four compounds are consistent with their stereochemical assignments. Also, endo PPAPs **81**−**83** and **87** (guttiferones A, C, D, and I) are reported to have C(7) δ values that are characteristic of exo compounds (41.0−41.2 ppm), although their H(8) $\Delta\delta$ values are consistent with their stereochemical assignments.[21,24] We regard the stereochemical assignments of all of these compounds as secure by virtue of NOE experiments and coupling constant analysis. Comparison of the NMR spectra of these PPAPs to those of PPAPs nearly identical to them (**30** to **25**,[27] **94** to **95**,[15] **98** and **99** to **100**,[28] and **81**−**83** and **87** to **84**−**86** and **88**[21,28−30]) suggests that the anomalous data may have been misreported or misassigned, although it remains possible that unique structural features in each of these compounds may contribute to the observed anomalies.

The structures assigned by Baggett et al. to guttiferone H (**103**) and its coisolate gambogenone (**115**) are unusual in that their skeletons cannot neatly be carved up into an acylphloroglucinol adorned by contiguous prenyl groups, but the structures appear to be secure by virtue of COSY and HMBC correlations.[31] These two compounds appear to have undergone extensive nonoxidative rearrangement after cyclization, although it is difficult to devise any reasonable sequence of steps by which **115** might form. Baggett et al.

Table 1. Type A PPAPs



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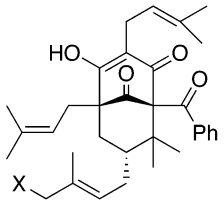

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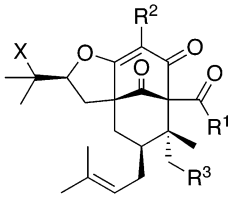
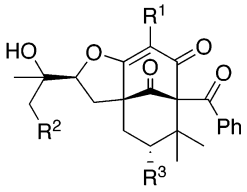
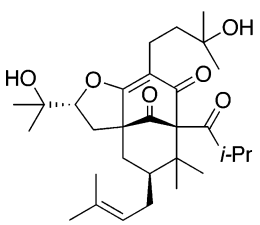


13–19



20–23

no.	R groups	name	source[a]	$[\alpha]_D$[b]
1	R^1 = *i*-Pr; R^2, R^3, R^4 = prenyl	hyperforin[40−42,c]	*H. perforatum*	+41 (e, 5)
2	R^1 = *s*-Bu; R^2, R^3, R^4 = prenyl	adhyperforin[43,d]	*H. perforatum*	NR
3	R^1 = *i*-Pr; R^2, R^3 = prenyl; R^4 = H	hyperevolutin A[44]	*H. revolutum* Vahl	+84.4 (m, 0.5)
4	R^1 = *s*-Bu; R^2, R^3 = prenyl; R^4 = H	hyperevolutin B[44 d]	*H. revolutum* Vahl	NR
5	R^1 = Ph; R^2 = H; R^3, R^4 = prenyl	nemorosone[6,10,11,45]	Cuban propolis *C. rosea* *C. grandiflora* *C. insignis* *C. nemorosa*	+113 (0.1) OMe: +150 (m, 0.8), +49 (1.4)
6	R^1 = 3-hydroxyphenyl; R^2 = H; R^3, R^4 = prenyl	hydroxynemorosone[10,11 e]	*C. nemorosa*	OMe: +143 (m, 0.7)
7	R^1 = Ph; R^2 = H; R^3 = isogeranyl; R^4 = prenyl	chamone I[45 d]	*C. grandiflora*	NR
8	R^1 = *i*-Pr; R^2 = H; R^3 = $CH_2CH_2CMe_2OH$; R^4 = prenyl	garcinielliptone A[46]	*G. subelliptica*	−33 (0.6)
9	R^1 = *s*-Bu; R^2 = H; R^3 = prenyl; R^4 = $CH_2CH_2CMe_2OH$	garcinielliptone D[46]	*G. subelliptica*	−22 (0.1)
10	R^1 = *s*-Bu; R^2 = H; R^3 = prenyl; R^4 = (*E*)-CH=CHCMe$_2$OH	garcinielliptone F[17]	*G. subelliptica*	−23 (0.09)
11	X = H	plukenetione D/E[10 f]	*C. nemorosa* *C. plukenetii*	OAc: +34.5 (0.03), −37.6 (0.1) OMe: +10.7 (3.1)
12	X = OAc	insignone[g]	*C. insignis*	OMe: +92.7 (1.6)
13	R^1 = Ph; R^2 = prenyl; R^3 = H; X = OH	hyperibone G[13]	*H. scabrum*	−29.3 (0.9)
14	R^1 = Ph; R^2 = prenyl; R^3 = H; X = OH (enantiomer)	propolone D[34]	Cuban propolis	+48.5 (0.7)
15	R^1 = Ph; R^2 = $CH_2CH(OH)CMe{=}CH_2$; R^3 = H; X = OH	hyperibone D[13 d]	*H. scabrum*	−61.9 (0.7)
16	R^1 = *i*-Pr; R^2 = prenyl; R^3 = H; X = OH	garsubellin A[14,15]	*G. subelliptica*	−21 (e, 1.1)
17	R^1 = *s*-Bu; R^2 = prenyl; R^3 = H; X = OH	garsubellin B[15 d]	*G. subelliptica*	−36 (e, 0.6)
18	R^1 = *i*-Pr; R^2, R^3 = prenyl; X = OH	furohyperforin[47 j]	*H. perforatum*	+62.4 (0.9) +81.9 (0.9, m) +68 (0.2)
19	R^1 = *i*-Pr; R^2, R^3 = prenyl; X = OOH	33-deoxy-33-hydroperoxy-furohyperforin[48]	*H. perforatum*	+75 (1.2)
20	R^1 = $CH_2CH(OH)CMe{=}CH_2$; R^2 = H; R^3 = (*E*)-CH=CHCMe$_2$OH	hyperibone E[13 d,h]	*H. scabrum*	−56.0 (0.2)
21	R^1 = prenyl; R^2 = H; R^3 = (*E*)-CH=CHCMe$_2$OH	hyperibone F[13 h]	*H. scabrum*	−31.0 (0.2)
22	R^1, R^2, R^3 = prenyl	sampsonione K[d,i]	*H. sampsonii*	−5.6 (1.1)
23	R^1, R^3= prenyl; R^2 = H	sampsonione L[i]	*H. sampsonii*	+55 (0.06)



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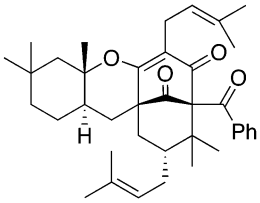

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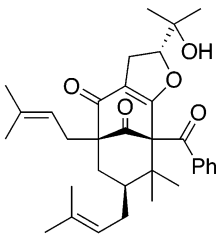
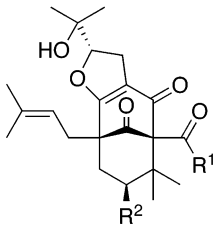


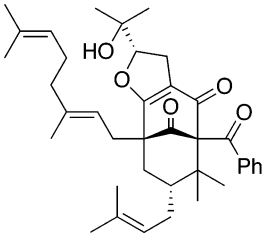
26

no.	name	source[a]	$[\alpha]_D$[b]
24	garcinielliptone C[46]	*G. subelliptica*	−40 (0.2)
25	no name[25]	*C. obdeltifolia*	+30.9 (0.3)
26	propolone C[34]	Cuban propolis	+35.7 (0.2)

Table 1 (Continued)



27–30



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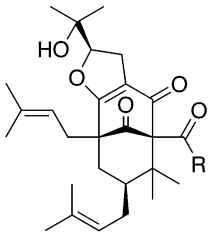
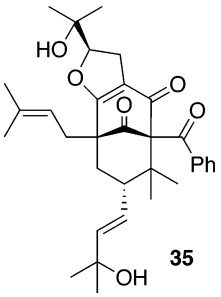
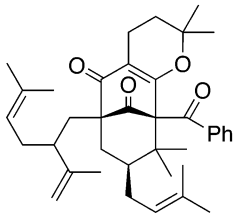


32–34



35

no.	R groups	name	source[a]	$[\alpha]_D$[b]
27	R^1 = *i*-Pr; R^2 = prenyl	garsubellin D[15]	*G. subelliptica*	−12 (e, 0.4)
28	R^1 = *s*-Bu; R^2 = prenyl	garsubellin E[15]	*G. subelliptica*	−7 (e, 0.4)
29	R^1 = Ph; R^2 = prenyl	hyperibone B[13,34]	*H. scabrum*	−20.8 (0.5) −42.2 (0.1)
30	R^1 = 3,4-dihydroxyphenyl; R^2 = (*R*)-isogeranyl	garcinielliptone FB[26]	*G. subelliptica*	−66 (0.2)
31		sampsonione M[i]	*H. sampsonii*	+55 (0.04)
32	R = *i*-Pr	garsubellin C[14,15]	*G. subelliptica*	+39 (e, 0.4)
33	R = Ph	hyperibone A[13,34]	*H. scabrum*	+57 (0.2) +63.7 (0.4)
34	R = Ph (enantiomer)	garcinielliptone I[17 k]	*G. subelliptica*	−37.7 (1.1)
35		hyperibone C[13 h]	*H. scabrum*	−27.3 (0.3)



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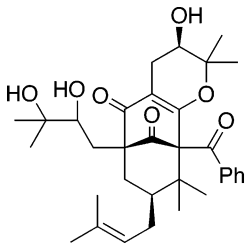

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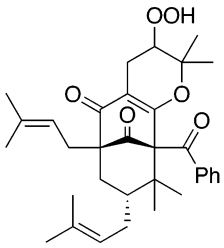

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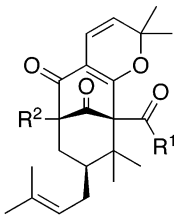
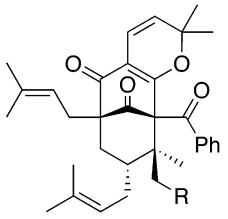
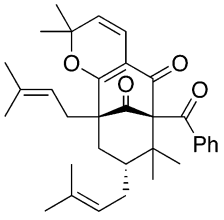


39–40

no.	R groups	name	source[a]	$[\alpha]_D$[b]
36		chamone II[45 d]	*C. grandiflora*	NR
37		propolone B[34 d]	Cuban propolis	+38.2 (0.6)
38		15,16-dihydro-16-hydroperoxy-plukenetione F[d,l]	*C. havetiodes* var. *stenocarpa*	+24.7 (0.3)
39	R^1 = *i*-Pr; R^2 = methyl	papuaforin B[49]	*H. papuanum*	NR
40	R^1 = Ph; R^2 = prenyl	scrobiculatone B[g]	*C. scrobiculata*	+44.7 (0.2)



41–42



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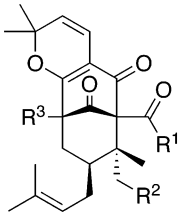
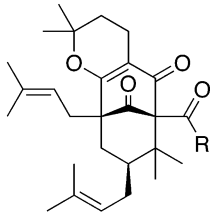


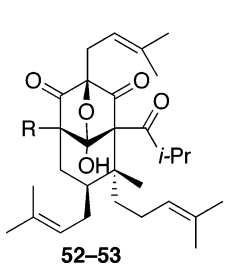
44–49

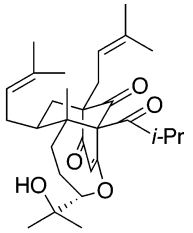


50–51

no.	R groups	name	source[a]	$[\alpha]_D$[b]
41	R = H	plukenetione F[f,m]	*C. plukenetii*	−53.6 (0.03)
42	R = prenyl	hypersampsone F[19 h]	*H. sampsonii*	+30 (0.2)
43		plukenetione G[f,m]	*C. plukenetii*	NR
44	R^1 = *i*-Pr; R^2, R^3 = prenyl	pyrano[7,28-*b*]hyperforin[50]	*H. perforatum*	+83.5 (0.3)
45	R^1 = Ph; R^2 = H; R^3 = prenyl	scrobiculatone A[49 g]	*C. scrobiculata*	+44.7 (0.2)
46	R^1 = *i*-Pr; R^2 = H; R^3 = CH_3	papuaforin A[49]	*H. papuanum*	+13 (0.1, m)
47	R^1 = *s*-Bu; R^2 = H; R^3 = CH_3	papuaforin C[49 d]	*H. papuanum*	+23 (0.1, m)
48	R^1 = *s*-Bu; R^2 = prenyl; R^3 = CH_3	papuaforin D[49 d]	*H. papuanum*	+64 (0.1, m)
49	R^1 = *i*-Pr; R^2 = prenyl; R^3 = CH_3	papuaforin E[49]	*H. papuanum*	+41 (0.1, m)
50	R = Ph	propolone A[37]	Cuban propolis	+40 (0.1)
51	R = *i*-Pr	garcinielliptone B[46]	*G. subelliptica*	−23 (0.1)

Table 1 (Continued)


52–53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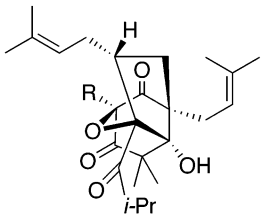
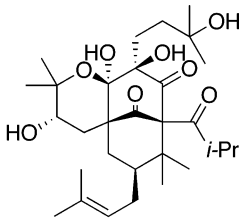

55–56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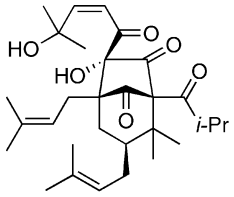
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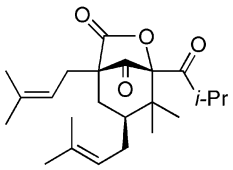
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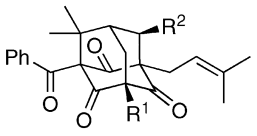
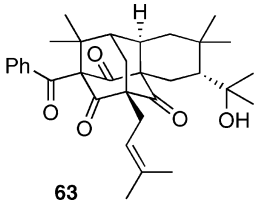
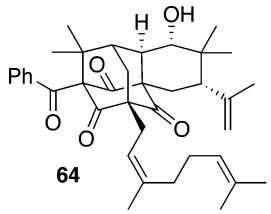

60–62


63

no.	R groups	name	source[a]	$[\alpha]_D$[b]
52	R = prenyl	8-hydroxyhyperforin-8,1-hemiacetal[48]	*H. perforatum*	+34 (1.0)
53	R = CH_3	hyperibone J[16]	*H. scabrum*	+16.9 (0.3)
54		oxepahyperforin[48]	*H. perforatum*	−73.7 (0.8)
55	R = prenyl	garcinielliptin oxide[n]	*G. subelliptica*	+1 (0.3)
56	R = $CH_2CH_2CMe_2OH$	garcinielliptone E[46]	*G. subelliptica*	−51 (0.2)
57		garcinielliptone H[17]	*G. subelliptica*	−14.3 (0.1)
58		garcinielliptone G[17]	*G. subelliptica*	−53 (0.1)
59		garcinielliptone J[17]	*G. subelliptica*	−166 (0.2)
60	R^1 = prenyl; R^2 = CH=CMe_2	plukenetione A[o]	*C. plukenetii*	+1 (0.8)
61	R^1 = prenyl; R^2 = (*S*)-2,2-dimethyloxiranyl	28,29-epoxyplukenetione A[l]	*C. havetiodes* var. *stenocarpa*	−4.4 (1.0)
62	R^1 = geranyl; R^2 = (*S*)-2,2-dimethyloxiranyl	sampsonione J[i]	*H. sampsonii*	+1.48 (0.2)
63		no name[25]	*C. obdeltifolia*	+10.0 (0.4)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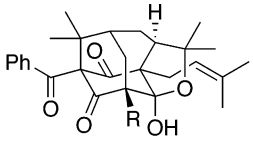
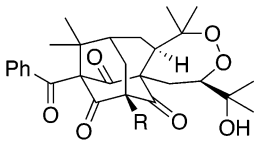
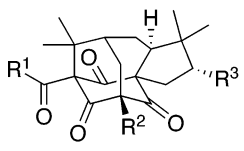
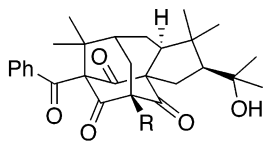

65–66


67–68

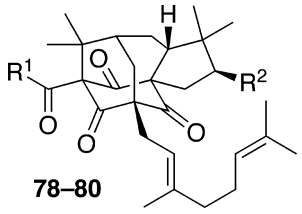
no.	R groups	name	source[a]	$[\alpha]_D$[b]
64		sampsonione I[i]	*H. sampsonii*	+16.88 (0.1)
65	R = geranyl	sampsonione A[p]	*H. sampsonii*	−49 (0.4)
66	R = prenyl	sampsonione B[p]	*H. sampsonii*	NR
67	R = prenyl	plukenetione C[f,l]	*C. plukenetii*	+65.9 (0.1)
68	R = (*E*)-CH=$CHCMe_2OOH$	33-hydroperoxyiso-plukenetione C[l]	*C. havetiodes* var. *stenocarpa*	−3.9 (0.2)


69–75


76–77

no.	R groups	name	source[a]	$[\alpha]_D$[b]
69	R^1 = Ph; R^2 = prenyl; R^3 = CMe_2OH	plukenetione B[f]	*C. plukenetii*	+17.2 (0.03)
70	R^1 = Ph; R^2 = geranyl; R^3 = *i*-Pr	hypersampsone D[19]	*H. sampsonii*	−35 (0.2)
71	R^1 = *i*-Pr; R^2 = geranyl; R^3 = CMe=CH_2	hypersampsone A[19]	*H. sampsonii*	+21 (0.3)
72	R^1 = Ph; R^2 = geranyl; R^3 = CMe_2OH	sampsonione C[q]	*H. sampsonii*	+13 (0.2)
73	R^1 = Ph; R^2 = geranyl; R^3 = isopropenyl	sampsonione D[q]	*H. sampsonii*	+12 (0.2)
74	R^1 = Ph; R^2 = geranyl; R^3 = O (ketone)	sampsonione E[q]	*H. sampsonii*	+57.7 (0.03)
75	R^1 = Ph; R^2 = geranyl; R^3 = H	sampsonione H[q]	*H. sampsonii*	+5.2 (0.07)
76	R = geranyl	sampsonione F[q]	*H. sampsonii*	+14.5 (1.1)
77	R = prenyl	sampsonione G[q]	*H. sampsonii*	+10.0 (0.01)

Table 1 (Continued)



78–80

no.	R groups	name	source[a]	$[\alpha]_D$[b]
78	R^1, R^2 = *i*-Pr	hypersampsone B[19]	*H. sampsonii*	+12 (0.3)
79	R^1 = *i*-Pr; R^2 = H	hypersampsone C[19]	*H. sampsonii*	+14.3 (0.2)
80	R^1 = Ph; R^2 = *i*-Pr	hypersampsone E[19]	*H. sampsonii*	+39 (0.2)

[a] *C.* = *Clusia*, *G.* = *Garcinia*, *H.* = *Hypericum*. [b] OMe or OAc indicates the specific rotation was measured for that derivative. The values in parentheses are the concentration and the solvent (e = EtOH, m = MeOH, no indication = $CHCl_3$). NR = not reported. [c] The absolute configuration is known to be as shown. [d] Not all of the stereocenters' configurations have been assigned. [e] The positions of the two bridgehead groups have been swapped from where they were placed in the original literature reports;[10,11] see text. [f] Henry, G. E.; Jacobs, H.; Sean-Carrington, C. M.; McLean, S.; Reynolds, W. F. *Tetrahedron* **1999**, *55*, 1581. [g] Porto, A. L. M.; Machado, S. M. F.; de Oliveira, C. M. A.; Bittrich, V.; Amaral, M. C. E.; Marsaioli, A. J. *Phytochemistry* **2000**, *55*, 755. [h] The stereochemistry of the C(7) substituent has been reassigned on the basis of the NMR spectra;[18] see text. [i] Hu, L. H.; Sim, K., Y *Org. Lett.* **1999**, *1*, 879. [j] Trifunovic, S.; Vajs, V.; Macura, S.; Juranic, N.; Djarmati, Z.; Jankov, R.; Milosavljevic, S. *Phytochemistry* **1998**, *49*, 1305. [k] The originally assigned relative configuration[17] has been corrected; see text. [l] Christian, O. E.; Henry, G. E.; Jacobs, H.; McLean, S.; Reynolds, W. F. *J. Nat. Prod.* **2001**, *64*, 23. [m] The stereochemistry was assigned according to the method of Grossman and Jacobs.[18] [n] Lin, C.-N.; Kiang, C.-W.; Lu, C.-M.; Wu, R.-R.; Lee, K.-H. *Chem. Commun.* **1996**, 1315. [o] Henry, G. E.; Jacobs, H.; Carrington, C. M. S.; McLean, S.; Reynolds, W. F. *Tetrahedron Lett.* **1996**, *37*, 8663. [p] Hu, L. H.; Sim, K., Y *Tetrahedron Lett.* **1998**, *39*, 7999. [q] Hu, L. H.; Sim, K., Y *Tetrahedron Lett.* **1999**, *40*, 759.

report no NOE data for **103** or **115**, but a large H(7)−H(8) coupling constant (14.0 Hz) in **103** induces the authors to suggest reasonably that these H atoms must be anti in this compound. This suggestion requires that the C(7) prenyl group of **103** be exo. The C(7) δ value of **103** (47.6 ppm) is more consistent with an endo configuration at C(7), but, because **103** has a seven-membered ring fused to C(1)−C(8) of the bicyclo[3.3.1]nonane skeleton, the C(7) δ value of **103** may not be reliable as an indicator of configuration. As a result, we retain the C(7) exo assignment for **103**. The C(7) configuration in **115** remains unknown.

2.3. Tables of PPAPs

In the tables, the isogeranyl and ω-isogeranyl groups are defined as shown in Figure 4.

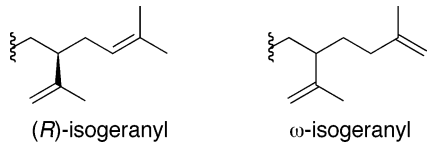


Figure 4. Isogeranyl and ω-isogeranyl groups.

To our knowledge, the only PPAPs for which absolute configurations have been determined experimentally are hyperforin,[32] xanthochymol,[33] and isoxanthochymol[33] (**1**, **88**, and **99**, respectively). Furthermore, some PPAPs (hyperibone G, **13**, and propolone D, **14**;[13,34] hyperibone A, **33**, and garcinielliptone I, **34**;[13,17,34] guttiferone E, **84**, and garcinol, **85**;[21,29,35−38] isoxanthochymol, **99**, and isogarcinol, **100**[21,28,29,31,35,36,39]) have been isolated in both enantiomeric forms. As a result, in the drawings in this review, we have arbitrarily chosen always to draw the C(9) ketone pointing toward the reader to make it easier to compare structures, but no information about absolute configuration should be inferred therefrom. Of course, a compound's specific rotation can reveal its absolute configuration, so we include each PPAP's specific rotation in the tables. These values should be used with some caution, a point that is illustrated by the discussion of Herath's "guttiferone I" (vide supra).

To reduce the difficulty of comparing the structures of different PPAPs, we encourage future authors of papers describing PPAPs to number one of the bridgehead C atoms (and not a ketone or enol C atom) as C(1), consistent with the IUPAC convention for numbering bicyclo[3.3.1]nonanes. We also *strongly* encourage future authors either to draw their C(1)−C(9) and C(5)−C(9) bonds as bold or hashed wedges, as in the tables, or to draw the PPAPs from the side-on perspective in which C(9) points "north" and C(3) and C(7) point "southwest" and "southeast", respectively.

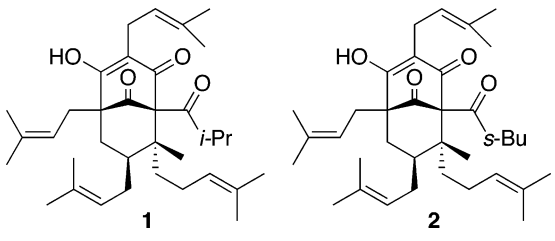
3. Biological Activity of PPAPs

In this section, the PPAPs that have been shown to have some biological activity are discussed. Many PPAPs have been found to possess moderate antioxidant, antiviral, or anticancer properties. Their ability to modulate the action of neurotransmitters associated with neuronal damaging and depression has also led to increasing interest in them.

3.1. Type A PPAPs

3.1.1. Hyperforin and Its Close Analogues

Hyperforin (**1**, Figure 5), a type A PPAP, is now thought to be responsible for much of the antidepressant activity of *H. perforatum* (St. Johns' wort).[56] The ancient Greeks used



1 **2**

Figure 5. Hyperforin and adhyperforin.

St. John's wort for its antidepressive properties as well as for treatment of skin injuries, burns, and neuralgia. In modern times, it has become very famous as a treatment for mild depression, anxiety, and schizophrenia. Clinical studies have shown St. John's wort to be as effective as a conventional synthetic antidepressant for treatment of mild to moderate depression,[57] but not effective in major depression.[58] In vitro studies show that both hyperforin (at concentrations of 0.1−1.0 μM) and its less abundant homologue adhyperforin (**2**)[43] inhibit the synaptosomal uptake of many neurotransmitters, including serotonin, dopamine, norepinephrine, γ-aminobutyric acid (GABA), and L-glutamate, when concentrations become low (IC_{50} = 1.1 μg/mL),[59] but it is still unclear if this mechanism is active in vivo.[59,60] Serotonin, dopamine, and norepinephrine balance mood and emotion, and GABA decreases anxiety and increases relaxation. By inhibiting the reuptake of these neurotransmitters, hyperforin increases their levels in the neural synapses, reinstates emotional balance, and improves mood. *H. perforatum* reveals not only antidepressant activity but also some side effects such as nausea, rash, fatigue, restlessness, photosensitivity, and acute neuropathy.[3]

Hyperforin has also long been known to have antibacterial activity.[42,59,61] A recent report on the inhibition of penicillin-resistant and methicillin-resistant *Staphylococcus aureus* has increased the interest in **1** as an antibacterial agent.[62]

Besides all of these positive effects of **1**, this natural product can repress some other drugs' effectiveness.[63,64] A recent study has shown that, when patients took St. John's wort together with the asthma drug theophylline, the anticlotting drug warfarin, birth control pills, or the immunosuppressant cyclosporine, the blood concentration levels of the latter drug decreased drastically. Hyperforin is a ligand for the pregnane X receptor, which regulates the expression of cytochrome P450, an enzyme involved in the oxidative metabolism of the above-mentioned drugs.[64,65] One should be alert to the side effects of herbal medicines and always make sure that the efficacy of prescribed drugs is not diminished by use of folk medicines.

Hyperforin is prone to air oxidation,[66] although its ammonium salt is more stable.[67] The products of the oxidation of **1** differ depending on the nature of the oxidant, the solvent, and the type of hyperforin used (ammonium salt or free acid form).[67] If **1** is treated with peroxidic reagents, the main organic product is the hemiacetal **52**, formed possibly through a C(3)-hydroxylated intermediate (Figure 6). When nonperoxidic reagents are used, a mixture of products is formed, the main ones being furan and pyran derivatives, **120** and **44**, respectively.

As is true of many β-hydroxyenones, hyperforin may be O- or C-alkylated when treated with an alkylating agent (Figure 7).[41,67] O-Methylation occurred when **1** was treated with methanol under Mitsunobu conditions or with diazomethane, whereas C-methylation occurred when **1** was treated with MeI.

A variety of acylated, alkylated, and oxidized derivatives of **1** were the subject of structure−activity studies with respect to inhibition of neurotransmitter uptake.[67] All derivatives studied were less potent than **1**, with IC_{50} values >10 μg/mL. These results are in accordance with the findings of other authors that suggest that removing the β-hydroxyenone group of **1** dramatically reduces its biological activity.[47,48,50] The mechanism of action of **1** and its derivatives is not fully understood, and more studies are required to determine structure−activity relationships in this class of compounds.

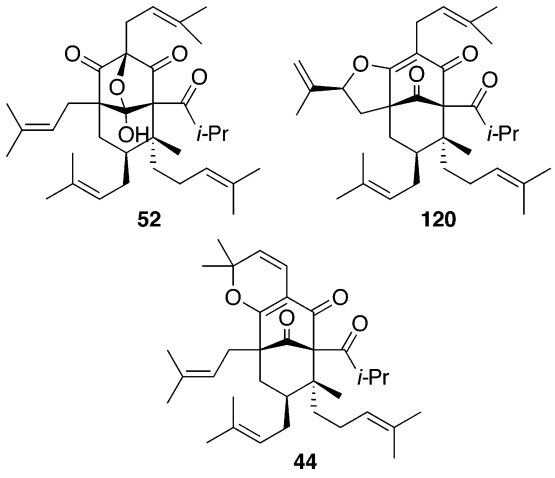


Figure 6. Products of oxidation of **1**.

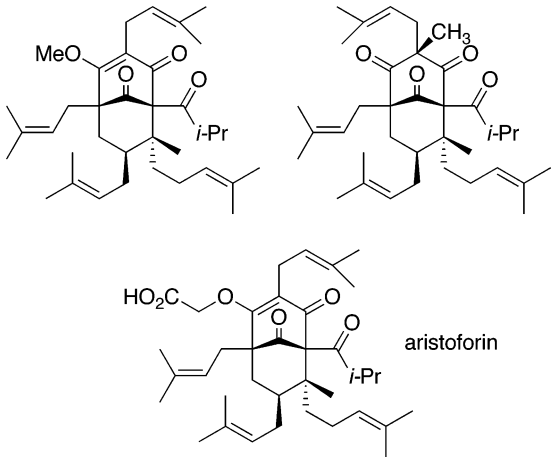
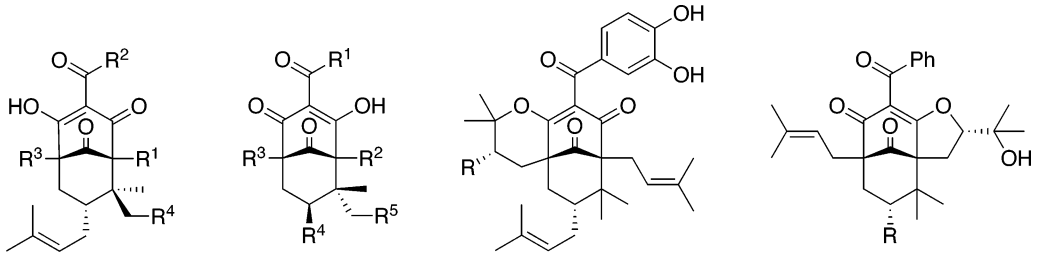


Figure 7. Products of alkylation of **1**.

Hyperforin has also recently been found to induce apoptosis in 10 human and 7 rat cancer cell lines, with IC_{50} values of 3−15 μM,[68] and in K562 and U937 leukemia cells, LN229 brain glioblastoma cells, and normal human astrocytes, with GI_{50} values of 14.9−19.9 μM.[69] Interestingly, hypericin, a polyaromatic also isolated from *H. perforatum*, and hyperforin together exert a growth inhibitory effect on K562 and U937 leukemia cells that is much larger than that exerted by either compound individually (2.0 μM **1**, 6.0 and 2.1%; 10.0 μM hypericin, 22.3 and 0.6%; combined, 43.6 and 20.2%).[69] Aristoforin (Figure 7), a derivative of **1** that is O-alkylated with a CH_2CO_2H group, has approximately equal antitumor activity to **1** in MT-450 cells and in rats with MT-450 cell-derived tumors, and it exhibits improved solubility and stability over **1**.[70] The ethyl ester of aristoforin has no such activity. Moreover, hydrogenation of both **1** and aristoforin over Pd/C leads to octahydro derivatives that have potent apoptotic and antiproliferative activity in MT-450 cells but no antitumor activity in rats, suggesting that conversion of the prenyl groups to isoamyl groups affects a change in transport properties, metabolism, or affinity for targets.

A mixture of hyperevolutin A and a small amount of hyperevolutin B (**3** and **4**, Figure 8) has been found to inhibit the growth of Co-115 colon tumor cells with an ED_{50} value of 2 μM.[44]

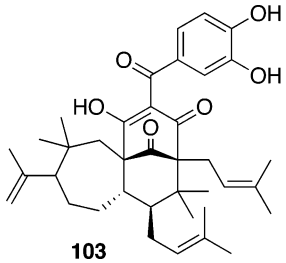
Table 2. Type B PPAPs



81–92 **93–97** **98–100** **101–102**

no.	R groups	name	source[a]	$[\alpha]_D$[b]
81	R^1 = 3,4-$(HO)_2C_6H_3$; R^2, R^3, R^4 = prenyl	guttiferone A[21,23]	*S. globulifera* *G. livingstonei* *G. humilis*	+34 (1.7)
82	R^1 = 3,4-$(HO)_2C_6H_3$; R^2, R^4 = prenyl; R^3 = ω-isogeranyl	guttiferone C[c]	*S. globulifera*	as mix with **83**: +92 (0.9)
83	R^1 = 3,4-$(HO)_2C_6H_3$; R^2, R^4 = prenyl; R^3 = isogeranyl	guttiferone D[c]	*S. globulifera*	as mix with **82**: +92 (0.9)
84	R^1 = 3,4-$(HO)_2C_6H_3$; R^2 = prenyl; R^3 = (*S*)-isogeranyl; R^4 = H	guttiferone E[21,37,38]	Cuban propolis *C. rosea* *G. ovafolia*	+101 (0.5)
85	R^1 = 3,4-$(HO)_2C_6H_3$; R^2 = prenyl; R^3 = (*S*)-isogeranyl; R^4 = H (enantiomer)	garcinol (camboginol)[29,35,36]	*G. cambogia* *G. indica*	−138 (0.1)
86	R^1 = 3,4-$(HO)_2C_6H_3$; R^2 = prenyl; R^3 = (*R*)-isogeranyl; R^4 = H	guttiferone F[30]	*Allanblackia stuhlmannii*	−293 (0.4)
87	R^1 = 3,4-$(HO)_2C_6H_3$; R^2 = prenyl; R^3 = geranyl; R^4 = H	guttiferone I[24,d]	*G. griffithii*	−68 (1.2)
88	R^1 = 3,4-$(HO)_2C_6H_3$; R^2 = prenyl; R^3 = (*S*)-ω-isogeranyl; R^4 = H	xanthochymol[31,33,37−39,51 e,f]	Cuban propolis *G. xanthochymus* *G. mannii* *G. staudtii* *G. subelliptica* *Rheedia madrunno*	+138 (0.1)
89	R^1 = CH_3; R^2 = Ph; R^3 = prenyl; R^4 = H	hyperibone L[16]	*H. scabrum*	+69.5 (0.2)
90	R^1 = CH_3; R^2 = *i*-Pr; R^3 = prenyl; R^4 = H	hyperpapuanone[49]	*H. papuanum*	+15 (0.1, m)
91	R^1, R^3 = prenyl; R^2 = Ph; R^4 = H	7-*epi*-clusianone[27,52,g]	*C. sandinensis* *C. torresii*	+62.3 (1.1)
92	R^1 = $CHPhCH_2CO_2H$; R^2 = *i*-Bu; R^3 = prenyl; R^4 = H	laxifloranone[53,c]	*Marila laxiflora*	+23.6 (m, 0.8)
93	R^1 = 3,4-dihydroxyphenyl; R^2, R^3, R^4 = prenyl; R^5 = H	aristophenone[20,31,h]	*G. xanthochymus*	+58 (0.1) OAc: +53 (0.1), +54 (0.1)
94	R^1 = Ph; R^2, R^3, R^4 = prenyl; R^5 = H	clusianone[11,27,i]	*C. congestiflora* *C. spiritu-sanctensis* *C. torresii*	+58.3 (0.7) OMe: +61 (1.4)
95	R^1 = Ph; R^2, R^4 = prenyl; R^3 = isogeranyl; R^5 = H	spiritone[c,j]	*C. spiritu-sanctensis*	NR
96	R^1 = 3,4-dihydroxyphenyl; R^2 = prenyl; R^3, R^4 = geranyl; R^5 = H	guttiferone B[21]	*S. globulifera*	−44 (0.5)
97	R^1 = 3,4-dihydroxyphenyl; R^2, R^3, R^5 = prenyl; R^4 = geranyl	guttiferone G[22,23]	*G. humilis* *G. macrophylla*	−25 (0.04) +8.7 (1.5)
98	R = prenyl	isogarcinol (cambogin)[29,35,36 h]	*G. indica* *G. cambogia* *G. pedunculata*	−224 (m, 0.1)
99	R = prenyl (enantiomer)	isoxanthochymol[21,28,31,39 e]	*G. pyrifera* *G. subelliptica* *G. xanthochymus* *G. ovafolia*	+181 (e, 0.6)
100	R = $CH_2CH_2CMe{=}CH_2$	cycloxanthochymol[28,39]	*G. pyrifera*, *G. subelliptica*	as 2:3 mix with **99**: +158 (m, 0.1)
101	R = (*E*)-$CH{=}CHCMe_2OH$	hyperibone H[13 k]	*H. scabrum*	+12.4 (0.4)
102	R = prenyl	hyperibone I[13 k]	*H. scabrum*	+13.3 (0.3)

Table 2 (Continued)



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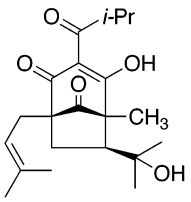

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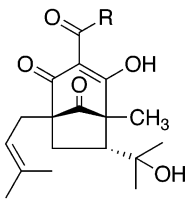
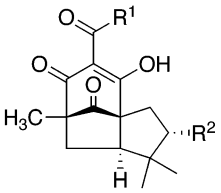
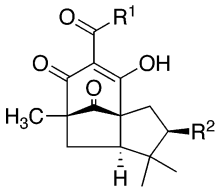


105–106

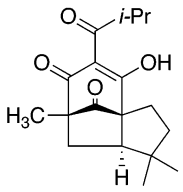


107–109

no.	R groups	name	source[a]	$[\alpha]_D$[b]
103		guttiferone H[31 c,l]	*G. xanthochymus*	+94 (0.006)
104		enaimeone A[54]	*H. papuanum*	+27.8 (0.1, m)
105	R = *i*-Pr	enaimeone B[54]	*H. papuanum*	+29.4 (0.1, m)
106	R = *s*-Bu	enaimeone C[54,c]	*H. papuanum*	+32.9 (0.1, m)
107	R^1 = *i*-Pr; R^2 = CMe=CH_2	ialibinone A[55]	*H. papuanum*	−22 (0.1)
108	R^1 = *s*-Bu; R^2 = CMe=CH_2	ialibinone C[55,c]	*H. papuanum*	−26 (0.1)
109	R^1 = *i*-Pr; R^2 = CMe_2OH	1′-hydroxyialibinone A[54]	*H. papuanum*	+3.7 (0.1, m)



110–113



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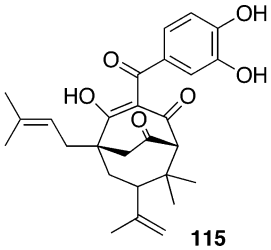

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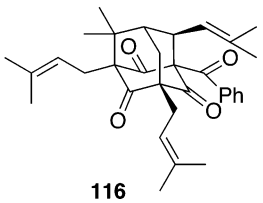
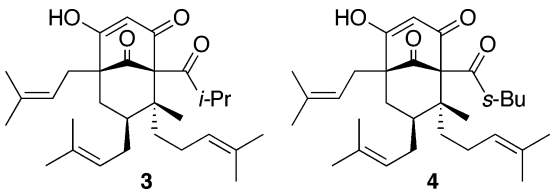


116

no.	R groups	name	source[a]	$[\alpha]_D$[b]
110	R^1 = *i*-Pr; R^2 = CMe=CH_2	ialibinone B[55]	*H. papuanum*	−91 (0.1)
111	R^1 = *s*-Bu; R^2 = CMe=CH_2	ialibinone D[55 c]	*H. papuanum*	−72 (0.1)
112	R^1 = *i*-Pr; R^2 = CMe_2OH	1′-hydroxyialibinone B[54]	*H. papuanum*	−35.7 (0.1, m)
113	R^1 = *s*-Bu; R^2 = CMe_2OH	1′-hydroxyialibinone D[54 c]	*H. papuanum*	−30.3 (0.1, m)
114		ialibinone E[55]	*H. papuanum*	−33 (0.1)
115		gambogenone[31 c]	*G. xanthochymus*	−5 (0.003, m)
116		hyperibone K[16]	*H. scabrum*	+22.3 (0.3)

[a] *C.* = *Clusia*, *G.* = *Garcinia*, *H.* = *Hypericum*, *S.* = *Symphonia*. [b] OMe or OAc indicates the specific rotation was measured for that derivative. The values in parentheses are the concentration and the solvent (e = EtOH, m = MeOH, no indication = $CHCl_3$). [c] Not all of the stereocenters' configurations have been assigned. [d] Two different compounds reported almost simultaneously have both been named guttiferone I, but one is probably identical to guttiferone G; see text.[22,24] [e] The absolute configuration is known and is opposite to what is shown. [f] Karanjgoakar, C. G.; Rao, A. V. R.; Venkataraman, K.; Yemul, S. S.; Palmer, K. J. *Tetrahedron Lett.* **1973**, 4977. Blount, J. F.; Williams, T. H. *Tetrahedron Lett.* **1976**, 2921. [g] Delle Monache, F.; Delle Monache, G.; Gacs-Baitz, E. *Phytochemistry* **1991**, *30*, 2003. Santos, M. H.; Speziali, N. L.; Nagem, T. J.; Oliveira, T. T. *Acta Crystallogr. C* **1998**, *54*, 1990. [h] The absolute configuration is known to be as shown. [i] McCandlish, L. E.; Hanson, J. C.; Stout, G. H. *Acta Crystallogr.* **1976**, *B.32*, 1793. [j] Porto, A. L. M.; Machado, S. M. F.; de Oliveira, C. M. A.; Bittrich, V.; Amaral, M. C. E.; Marsaioli, A. J. *Phytochemistry* **2000**, *55*, 755. [k] The stereochemistry of the C(7) substituent has been reassigned on the basis of the NMR spectra; see text.[18] [l] The stereochemistry of the C(9) bridge relative to the C(6) and C(7) substituents has been assigned on the basis of the H(6)−H(7) coupling constant; see text.[18] [k] The stereochemistry of the C(7) substituent has been reassigned on the basis of the NMR spectra; see text.[18]



3 **4**

Figure 8. Hyperevolutins A and B.

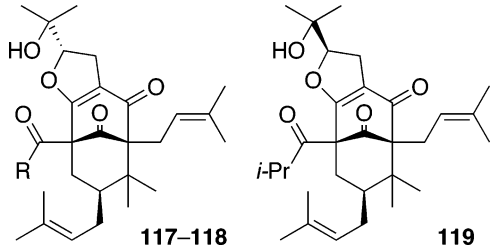
3.1.2. Nemorosone

Nemorosone (**5**), another type A PPAP, is found in the resins and latex of plants of *Clusia* (Clusiaceae) species.[45] Bees use these resins and latex to build their hives, at least partly because they make a good construction material for sealing openings in the hive and hardening the cell walls.[45] Propolis, an extract of beehives, has been known since ancient times as an antiseptic; in fact, Aristotle himself urged people to use it as a means to treat abscesses and wounds.[4] Studies on bee behavior have revealed that after bees kill heavy intruders, they cover them with propolis! Not being able to throw the corpses off the hives, the bees make sure that their nest will not develop a bacterial infection.

A large number of the constituents of propolis are derived from plants. There are over 200 chemical substances in propolis,[71] their ratio depending on the region from which the propolis is collected. In Europe, the major biological active constituents are flavonoids and cinnamic acid derivatives, whereas in tropical regions, the home of many *Clusia* plants, the major compounds are polyprenylated benzophenones such as PPAPs.[38] Despite the differences in their chemical composition, propolis samples from various geographical regions have always been found to be biologically active.[38]

Nemorosone is the major constituent of *Clusia* species resin that is responsible for its antimicrobial activity,

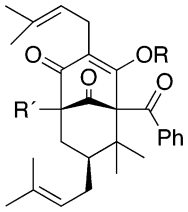
Table 3. Type C PPAPs



no.	R groups	name	source[a]	$[\alpha]_D$[b]
117	R = Ph	garcinielliptone K[12]	*G. subelliptica*	+27 (0.3)
118	R = *i*-Pr	garcinielliptone M[12]	*G. subelliptica*	+73 (0.2)
119		garcinielliptone L[12]	*G. subelliptica*	−41 (0.3)

[a] *G.* = *Garcinia*. [b] Values in parentheses are the concentrations (solvent is $CHCl_3$).

constituting about 50% of the resin by mass.[10,11] When a crude extract of *Clusia* species resin is methylated, *O*-methylnemorosone, 16-hydroxymethylnemorosone, and 7-*epi*-methylnemorosone (*O*-methylplukenetione D/E) are obtained.[10,11] Cuesta-Rubio has corrected the type C PPAP structure initially proposed for nemorosone[10,11] to **5** (Figure 9) and its tautomer by switching the originally assigned positions of the groups at the bridgeheads,[6] making it identical to the structure that has been called "nemorosone II".[10] Cuesta-Rubio has also shown that the structure of *O*-methylnemorosone is **5a**, and *O*-methylnemorosone II is the enol ether regioisomer.



compound	R	R´
5	H	prenyl
5a	Me	prenyl
36	H	isogeranyl

Figure 9. Nemorosone, *O*-methylnemorosone, and chamone II.

The bactericidal activities of both **5** and **5a** were studied, but the latter was not active.[38,45] The conclusion was that the enol form was necessary for nemorosone to be biologically active. Even the prenylation pattern proved to be essential for the antimicrobial effect of this type of natural products, as chamone II (**36)** was less effective than **5** as a bactericide against *Paenibacillus* honeybee pathogens.

Besides antimicrobial activity, nemorosone showed cytotoxicity and antioxidant activity.[38] The IC_{50} values of nemorosone against four cancer cell lines (3.3−7.2 μM) were comparable to those of doxorubicin. Nemorosone also targets DNA topoisomerases and telomerase, but to a much lower extent, the required concentration being 10−38 times higher than that necessary for a 50% inhibition of cellular growth. Compound **5a** showed much lower cytotoxic and antioxidant activities, the IC_{50} values being 10−30 times and 10 times higher, respectively, with respect to that of the reference.

Nemorosone showed an EC_{50} of 0.8 μM against HIV infection of C8166 human T lymphoblastoid cells.[27]

3.1.3. Garsubellin A

Garsubellin A (**16**, Figure 10) has been isolated from *Garcinia subelliptica*, a tree that grows in Okinawa.[15] Studies have shown garsubellin A to be an inducer of choline

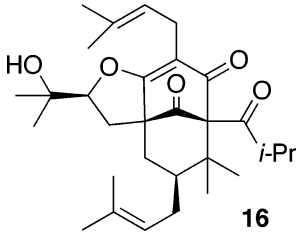


Figure 10. Garsubellin A.

acetyltransferase (ChAT) in P10 rat septal neuron cultures, increasing it by 154% at a 10 μM concentration.[14] Acetylcholine is a neurotransmitter, and a low concentration of this compound is associated with neurodegenerative diseases such as Alzheimer's disease. Garsubellin A also inhibits the release of β-glucuronidase and histamine, the 50% inhibition concentration (IC_{50} = 15.6 μM) being even lower than that of the reference mepacrine (IC_{50} = 20.6 μM).[46] This property is associated with antiinflamatory activity. Other phloroglucinol derivatives isolated from the same plant (garcinielliptones A−D, F, H, I, K−M) show little or no such activity.[12,17] The idea that garsubellin A might have potential for the treatment of Alzheimer's disease has led to an increased interest over the past decade in studying the biological activity and possible synthetic approaches to this class of compounds.

3.1.4. Other Type A PPAPs

Propolone A (**50**), 7-*epi*-clusianone (**91**), and clusianone (**95**) (Figure 11) were tested for their activity against HIV infection of C8166 human T lymphoblastoid cells.[27] Propolone A showed the best results, with an EC_{50} of 0.32 μM, followed by 7-*epi*-clusianone, with an EC_{50} of 2.0 μM. Clusianone was very active (EC_{50} = 0.02 μM), but it also showed increased cytotoxicity. The absence of a free enol in propolone A showed that this group was not essential to antiviral activity. Also, the different EC_{50} values of the two epimers, 7-*epi*-clusianone and clusianone, showed that the C(7) configuration was important to the PPAP's potency.

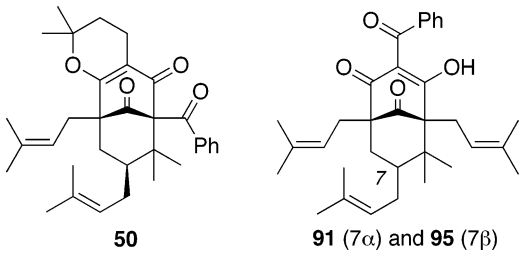


Figure 11. Propolone A, 7-*epi*-clusianone, and clusianone.

Propolone A (**50**) also showed antibacterial activity against two Gram-positive bacteria (*Streptomyces chartrensis* and *Streptomyces violochromogenes*), but it was not active against Gram-negative bacteria and yeasts.[37]

In a different study, 7-*epi*-clusianone (**91**) exhibited high in vitro activity against *Trypanosoma cruzi*, the microbe responsible for Chagas' disease, with an LC_{50} = 260 μM, 29 times higher than that of the drug used to treat this disease.[52] Unfortunately, it was inactive in in vivo studies in the mouse model. More studies with related natural or synthetic compounds are needed to find more active derivatives that could be used as chemoprophylactic agents.

Hyperibone J (**53**, Figure 12), a PPAP very close in structure to hyperforin-derived hemiacetal **52**, shows moder-

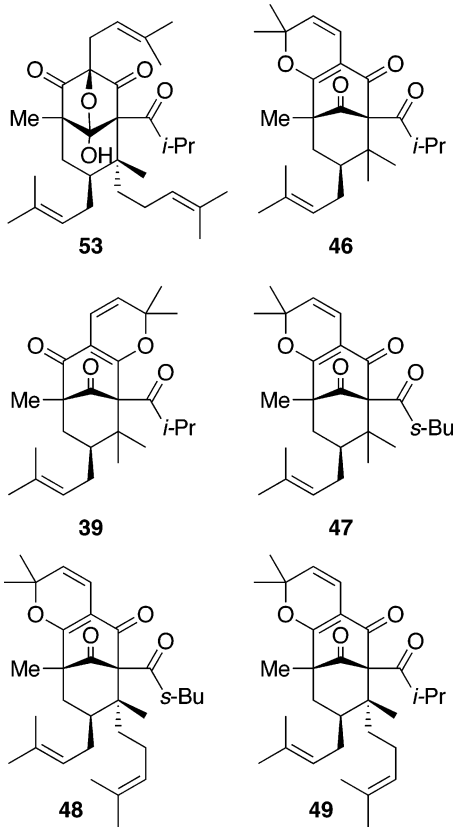


Figure 12. Hyperibone J and papuaforins A−E.

ate cytotoxicity against breast and lung tumor cells (IC_{50} = 17.8 and >20 μg/mL, respectively).[16]

Papuaforins A (**46**), B (**39**), and C−E (**47**−**49**), which are extracted from *Hypericum papuanum* (Papua New Guinea), show moderate cytotoxic activity against the KB cell line (IC_{50} = 4.9−13.0 μg/mL) and weak antibacterial activity toward three bacteria (*Micrococcus luteus*, *Staphylococcus epidermis*, and *Bacillus cereus*).

3.2. Type B PPAPs

3.2.1. Garcinol and Its Derivatives

Garcinol (**85**, Figure 13),[36] also known as camboginol, is extracted from *Garcinia indica* and several other plants as a yellow pigment.[28,35,72] The dried fruit rind is used in folk medicine and as a garnish for curry in India. Garcinol scavenges 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical (3 times more effectively than DL-α-tocopherol), hydroxyl radical (more effectively than DL-α-tocopherol), methyl radical, and superoxide anion.[73] These results suggest that garcinol can play an important role in the treatment of gastric

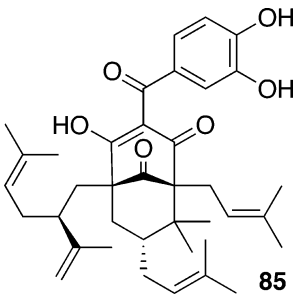


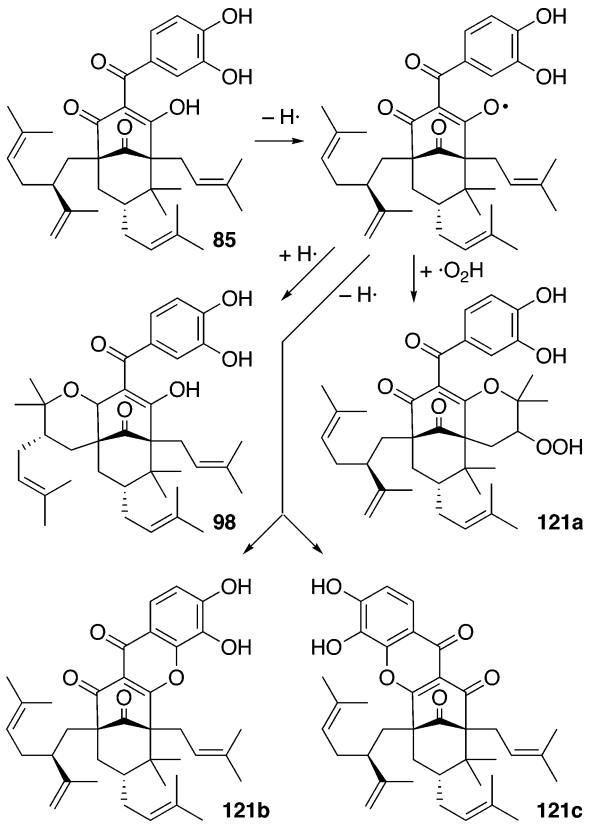
Figure 13. Garcinol (camboginol).

ulcers caused by the hydroxyl radical[74] or by a chronic infection with *Helicobacter pylori*, a global pathogen, which, together with cells from gastric mucous membrane, produces hydroxyl radicals and superoxide anions.[75] Nowadays, antibiotics such as clarithromycin are used to treat *H. pylori* infection, but there are some side effects when using antibiotics, such as the development of resistance. Garcinol may be a viable alternative to conventional antibiotics.

Garcinol shows antibiotic activity against methicillin-resistant *S. aureus* (MIC = 3−12 μg/mL) comparable to that of vancomycin (MIC = 6 μg/mL),[28] and it inhibits topoisomerases I and II (IC_{50} = 43 and 55 μg/mL, respectively) at concentrations comparable to that of etoposide (IC_{50} = 70 μg/mL for topoisomerase II).[76]

Sang et al. has recently reported the structure of some oxidation products of garcinol and has proposed mechanisms for the formation of these products (Scheme 1).[77,78] The reaction of garcinol with AIBN or the stable free DPPH radical generates a conjugated radical. Cyclization then occurs, involving the catechol ring or a pendant alkenyl group to give both compounds known to occur naturally (isogarcinol, **98**) and those that have not (yet) been isolated from natural sources (**121a**−**c**). Isogarcinol shows biological activities similar to those of garcinol; it has been claimed to be an antiinflammatory and antitumor compound, a lipase inhibitor, an antiobesity agent, and an antiulcer agent.[77] It also inhibits the growth of methicillin-resistant *S. aureus*.

Scheme 1. Oxidation Pathways of Garcinol



Garcinol, together with compounds **121b** and **121c**, proved to have good antitumor activity against human leukemia HL-60 cells, being more effective than curcumin, a well-known antioxidant used as a reference in these studies.[79] The possible chemotherapeutic property of garcinol was also tested on other cell lines (human promyelocytic HL-60 cells,

murine macrophage RAW 264.7 cells, and cyclin D1-positive cells), and the same positive effect was obtained. It inhibits histone acetyltransferases (HATs, $IC_{50} \approx 7\ \mu M$) and p300/CPB-associated factor (PCAF, $IC_{50} \approx 5\ \mu M$), both of which modulate gene expression. If HAT and/or histone deacetylase (HDAC) activities are altered, diseases such as cancer or neurodegenerative disease can develop.[80]

3.2.2. Guttiferones A–E, Xanthochymol, and Their Analogues

Xanthochymol (**88**) and guttiferone E (**84**) (Figure 14) are extracted as a mixture from *Garcinia* and *Clusia* species[30,39,51] and are said to be inseparable.[21] This mixture has strong inhibitory activity against tubulin depolymerization in vitro ($IC_{50} = 20\ \mu M$), comparable to that of paclitaxel ($IC_{50} = 0.5\ \mu M$), making it a possible inhibitor of cell replication. However, if the β-hydroxyenone or both phenolic OH groups are methylated, or if the double bonds are hydrogenated, a complete loss of activity is observed.[39] Some activity is retained if only one phenolic OH group is methylated. Unfortunately, the mixture shows no effect on whole cells, suggesting that it cannot cross the cell membrane or is deactivated by cellular processes.

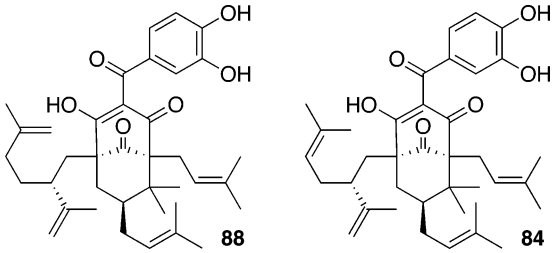


Figure 14. Xanthochymol and guttiferone E.

Pure xanthochymol shows an antibiotic activity against methicillin-resistant *S. aureus* (MIC = 6−25 μg/mL) comparable to that of vancomycin (MIC = 6 μg/mL),[28] and it inhibits topoisomerases I and II (IC_{50} = 33 and 40 μg/mL, respectively) at concentrations comparable to that of etoposide ($IC_{50} = 70\ \mu g/mL$ for topoisomerase II).[76]

Guttiferones A, B, E, C, and D (**81**, **97**, **84**, **82**, and **83**) (Figure 15), the latter two isolated as an inseparable mixture, were tested for anti-HIV biological activity.[21] All

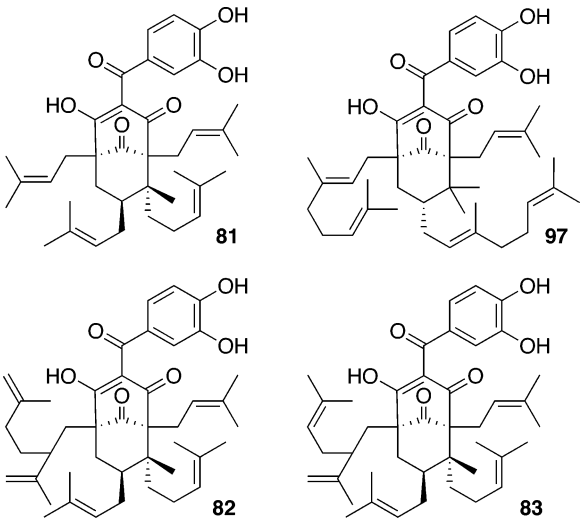


Figure 15. Guttiferones A, B, C, and D.

showed inhibitory effects on in vitro infection in human lymphoblastoid CEM-SS cells, with EC_{50} values of 1−10 μg/mL, but there was no indication of a decrease in indices of viral replication. In a different study, guttiferone F (**86**) showed both cytoprotection against HIV-1 in vitro (EC_{50} = 23 μg/mL) and cytotoxicity to the host cells ($IC_{50} = 82\ \mu g/mL$).[30]

Guttiferone E, xanthochymol, aristophenone (**94**), isoxanthochymol (**99**), and cycloxanthochymol (**100**, Figure 16) exhibit cytotoxic activity against SW-480 colon cancer cells (IC_{50} = 7.5−33.3 μM) and antioxidant activity in the DPPH free radical assay (IC_{50} = 53−125 μM).[31]

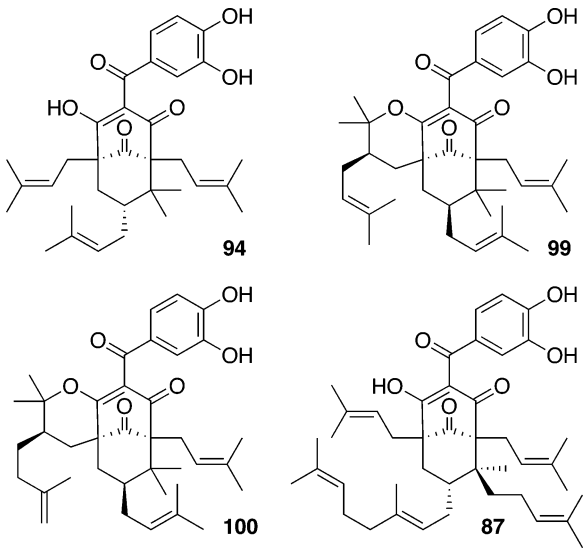


Figure 16. Aristophenone, isoxanthochymol, cycloxanthochymol, and guttiferone I.

Guttiferone I (**87**) inhibits the binding activity of α-liver X receptor (LXRα) but is less effective against β-receptor (LXRβ), with IC_{50} = 3.4 and >15 μM, respectively.[22] LXR agonists are therapeutical agents for the control of plasma cholesterol levels, increasing reverse cholesterol transport.

3.2.3. Ialibinones A–E and Their Analogues

Ialibinones A−E (**107**, **110**, **108**, **111**, and **114**) (Figure 17) were isolated from *H. papuanum*.[55] When tested for antibacterial activity, ialibinones C and D showed stronger activity than ialibinones A and B against *B. cereus* and *S. epidermis* but almost identical effectiveness against *M. luteus*. Ialibinone E was ineffective regardless of the bacteria used in the experiment.

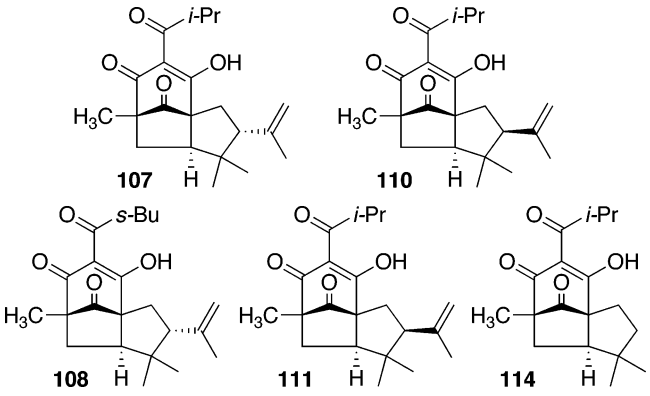


Figure 17. Ialibinones A−E.

The dried aerial parts of *H. papuanum* are traditionally used as a remedy for sores and wounds due to their antibacterial activity. The active components of this plant are hyperpapuanone, 1′-hydroxyialibinones A, B, and D, and enaimeones A−C (**90**, **109**, **112**, **113**, and **104**−**106**) (Figure 18).[49,54] 1′-Hydroxyialibinones A, B, and D show identical or slightly reduced antibacterial activity compared with the ialibinones A, B, and D, whereas hyperpapuanone has moderately potent antibacterial activity against *M. luteus*, *S. epidermis*, and *B. cereus*. The cytotoxicities of the 1′-hydroxyialibinones are 3−5 times weaker than those of the corresponding ialibinones. Enaimeones A−C have antibacterial activity similar to those of ialibinones A−C, but show a rather weak cytotoxicity against KB cells.

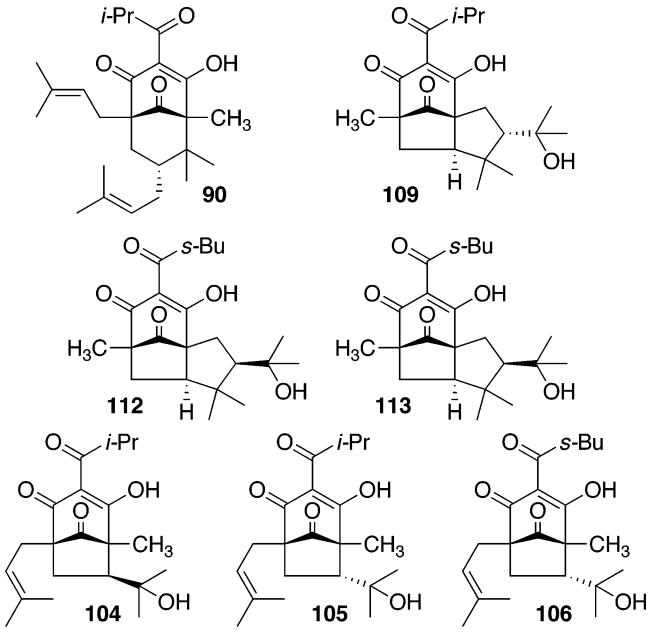


Figure 18. Hyperpapuanone, 1′-hydroxyialibinones A, B, and D, and enaimeones A−C.

3.2.4. Other Type B PPAPs

Laxifloranone (**92**, Figure 19) exhibits moderate inhibition of the cytopathic effects of HIV-1 in a human T-lymphoblastoid cell line (CEM-SS, $EC_{50} = 0.62$ μg/mL and $IC_{50} = 6.6$ μg/mL).[53] Hyperibones K and L (**116** and **89**) moderately inhibit breast ($IC_{50} = 10.0$ and 15.0 μM, respectively) and lung ($IC_{50} = 13.7$ and 9.2 μM, respectively) tumor cell replication, but they show no anti-HIV activity.[16]

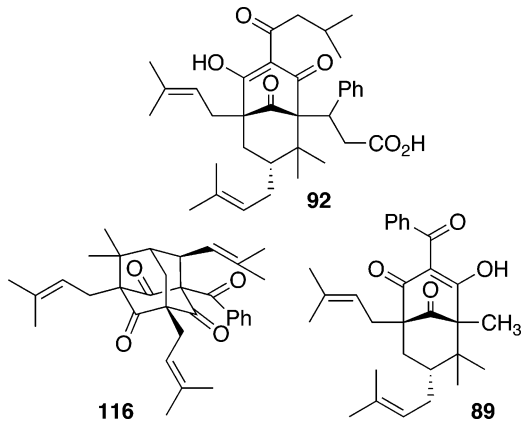


Figure 19. Laxifloranone and hyperibones K and L.

3.3. Type C PPAPs

Garcinielliptones L and M (**119** and **118**) (Figure 20), isolated from *G. subelliptica*, inhibit the release of β-glucuronidase and histamine (**119**, $IC_{50} = 22.9$ and >30 μg/mL; **118**, $IC_{50} = 13.6$ and 19.0 μg/mL), activity that makes them potential antiinflammatory agents.[12] Mepacrine, a positive control, has corresponding IC_{50} values of 13.6 and 23.3 μg/mL. The two garcinelliptones also have inhibitory effects on the accumulation of NO_2^- in the culture of RAW 264.7 and N9 cells and slight inhibitory effects on tumor necrosis factor α production in cultured RAW 264.7 cells. Garcinielliptone FB, isolated from the same plant, shows moderate cytotoxic activity against liver, breast, and colon cancer cell lines ($IC_{50} = 6.8$, 6.3, and 11.2 μg/mL, respectively).[26]

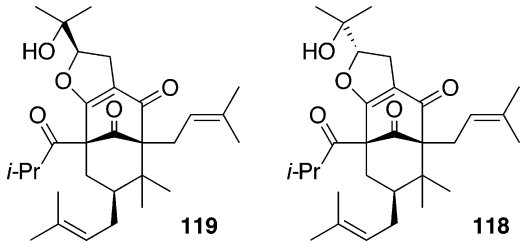
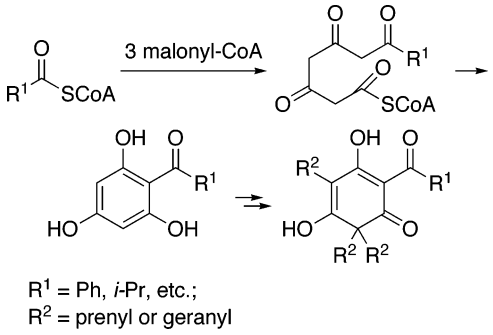


Figure 20. Garcinielliptones L and M.

4. Biosynthesis of PPAPs

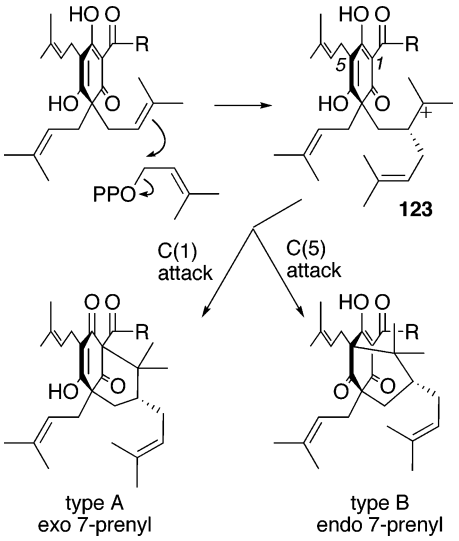
Early labeling experiments provided evidence for a polyketide-type biosynthesis for bitter acids that involves one acyl-CoA and three malonyl-CoA units (Scheme 2).[57,81] Similarly, numerous enzymologic studies showed that the biosynthesis of acylphloroglucinols involves condensation of three molecules of malonyl-CoA and one molecule of acyl-CoA. The product, a tetraketide, is subsequently cyclized by Dieckmann condensation into an acylphloroglucinol.[82] The prenylation or geranylation of this compound occurs through an enzyme-catalyzed addition of prenyl or geranyl pyrophosphate to the phloroglucinol moiety.[8,83]

Scheme 2. Biosynthesis of MPAPs



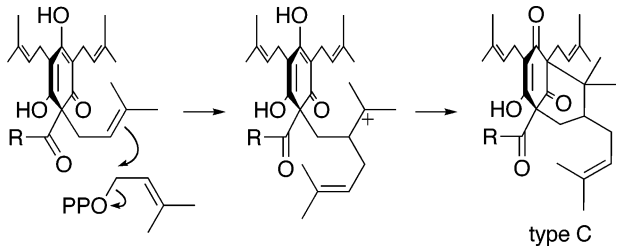
Cuesta-Rubio proposed that MPAPs are cyclized to both type A and type B PPAPs via a common precursor (Scheme 3).[6] Attack of one of the geminal prenyl groups of an MPAP on prenyl pyrophosphate gives the tertiary carbocation **123**. Attack of C(1) of **123** on the pendant carbocation (or the corresponding pyrophosphate) would provide a type A PPAP, whereas attack of C(5) would provide a type B PPAP. Moreover, a single diastereomer of **123** can lead to either a

Scheme 3. Cyclization of MPAPs To Give Type A or B PPAPs



type A PPAP with an exo 7-prenyl group or a type B PPAP with an endo 7-prenyl group. Most type A PPAPs have exo 7-prenyl groups, and most type B PPAPs have endo 7-prenyl groups. A similar mechanism is proposed for hyperforin biosynthesis.[57] The most likely scheme for the biosynthesis of the type C PPAPs, by contrast, would require that the initial MPAP have its quaternary center bear the acyl group (Scheme 4).

Scheme 4. Possible Biosynthesis of Type C PPAPs



5. Synthetic Efforts toward PPAPs

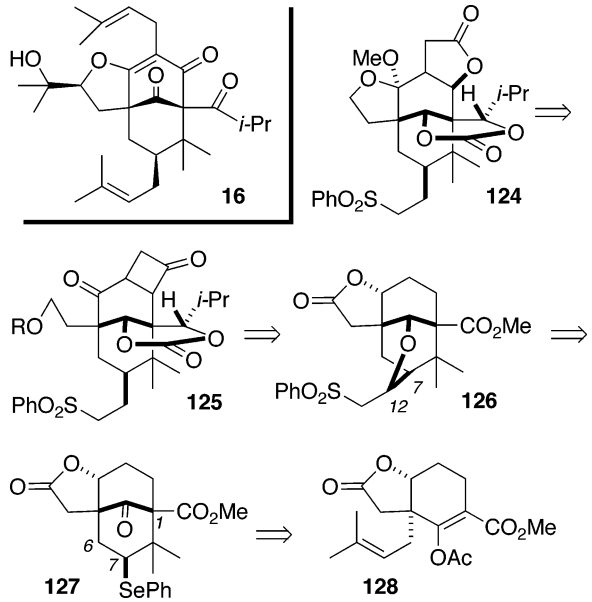
Many approaches to the synthesis of the 1-acylbicyclo-[3.3.1]nonane-2,4,9-trione structure of type A PPAPs have been reported in the past decade, but only near the end of 2005 have the first two and so far only total syntheses of any PPAP, garsubellin A by Shibasaki and Danishefsky, been reported.[84,85] All approaches have relied on the α,α′-annulation of a three-carbon bridge onto a cyclohexanone, although the methods used to execute this annulation differ dramatically. The methods most often used to form the two new C−C bonds have involved classical carbonyl chemistry. Shibasaki's first approach used an addition−elimination with a β-chloroacrylate derivative followed later by an aldol reaction,[86,87] Stoltz used a Claisen−Dieckmann reaction with malonyl chloride,[88] Kraus used two addition−elimination reactions with a diacetoxyvinyl sulfone,[89] and Nicolaou used a Michael−aldol reaction with methacrolein.[90] A variety of nonclassical approaches have also been used. Shibasaki's second and successfully completed approach to garsubellin A used an aldol reaction and an O-allylation to install vinyl and allyl groups at the α- and α′-positions of a cyclohexanone and then used a ring-closing metathesis to form the three-carbon bridge.[84] Danishefsky and Nicolaou used "biomimetic" electrophile-mediated cyclizations of a pendant prenyl group,[85,91] Young used an intramolecular [3 + 2] cycloaddition between an allene and a pendant nitrile oxide,[92] and Kraus and Mehta both used an intramolecular metal-catalyzed addition of a ketone to a pendant alkene.[93,94] Grossman used a mix of classical and nonclassical approaches to α,α′-annulation, with key steps of a lead-mediated alkynylation followed later by an aldol reaction.[95] Nicolaou's first approach and Danishefsky's approach were different because they annulated the three-carbon bridge containing the quaternary center (*gem*-dimethyl group) onto the cyclohexanone,[91] whereas all others annulated the three-carbon bridge containing the β-dicarbonyl moiety.

A fairly recent review by Butkus describes the stereocontrolled synthesis and reactions of bicyclo[3.3.1]nonanes.[96] This review will discuss synthetic approaches to bicyclo-[3.3.1]nonanes explicitly aimed at the PPAPs.

5.1. Nicolaou's Se-Mediated Electrophilic Cyclization Approach

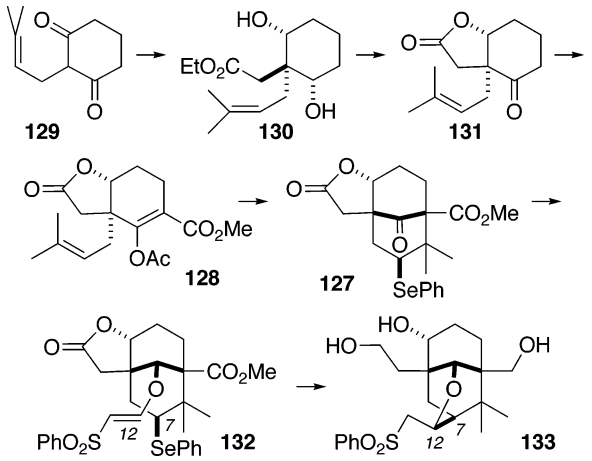
Nicolaou was the first to describe an effort to synthesize a PPAP.[91] The model compound **124** chosen by Nicoloau's group contained the key structural features of garsubellin A (**16**), including the extra ring fused to the bicyclic core (Scheme 5). The lactone ring of **124** would be formed by a Baeyer−Villiger reaction of cyclobutanone **125**, which would be derived from **126** via a [2 + 2] cycloaddition (among other steps). The C(7)−C(12) bond of **126** would be derived from C(7) selenide **127** via radical addition to an alkenyl sulfone, and the C(1)−C(6) bond of **127** would be constructed by electrophilic cyclization of the prenylated β-keto ester **128**.

Scheme 5. Nicolaou's Retrosynthesis of Garsubellin A



The synthesis of **124** began with C-alkylation of 1,3-diketone **129** and stereoselective reduction to give diol **130** (Scheme 6). Hydrolysis of the ester of **130**, lactonization with DCC and 4-DMAP, and oxidation of the remaining alcohol provided keto lactone **131**. Deprotonation of **131**, treatment with methyl cyanoformate, and acetylation gave enol acetate **128**. The key step of the synthesis, the selenium-mediated cyclization, occurred upon addition of $SnCl_4$ to a mixture of **128** and *N*-(phenylseleno)phthalimide at −23 °C to give

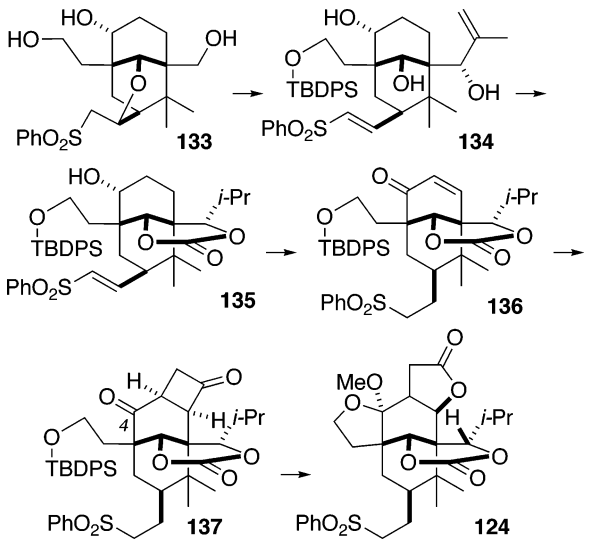
Scheme 6. Nicolaou's Approach to Garsubellin A, Part 1



bicyclo[3.3.1]nonane **127** in 95% yield. The PhSe group in **127** was placed exclusively in the thermodynamically favored exo orientation. Stereoselective reduction of the ketone of **127** provided a secondary alcohol, which was further converted to vinylogous sulfonate **132** upon addition of *trans*-1,2-bis(phenylsulfonyl)ethylene. Treatment of **132** with *n*-Bu_3SnH and AIBN formed the C(7)−C(12) bond, and global reduction gave triol **133**.

The least hindered hydroxyl group of **133** was protected, and the remaining primary alcohol was oxidized to the aldehyde (Scheme 7). Addition of *i*-PrMgBr resulted only in reduction of the aldehyde, but isopropenylmagnesium bromide not only added to the aldehyde with exquisite stereoselectivity but also promoted β-elimination of the β-alkoxy sulfone side chain to give triol **134**. Conditions to reduce both C=C π bonds of **134** could not be identified, so the isopropenyl group was reduced with H_2 and PtO_2, and addition of triphosgene and pyridine gave the cyclic carbonate **135**. Hydrogenation of **135** was then followed by oxidation of the remaining hydroxyl group to the ketone. Conversion of the ketone to the enone **136** proved to be challenging, and it could be accomplished only by addition of SeO_2 in AcOH at 110 °C. The light-promoted cycloaddition of dimethoxyethylene to **136** occurred regio- and stereoselectively from the exo face of the enone. The dimethoxyketal thus formed was converted to cyclobutanone

Scheme 7. Nicolaou's Approach to Garsubellin A, Part 2

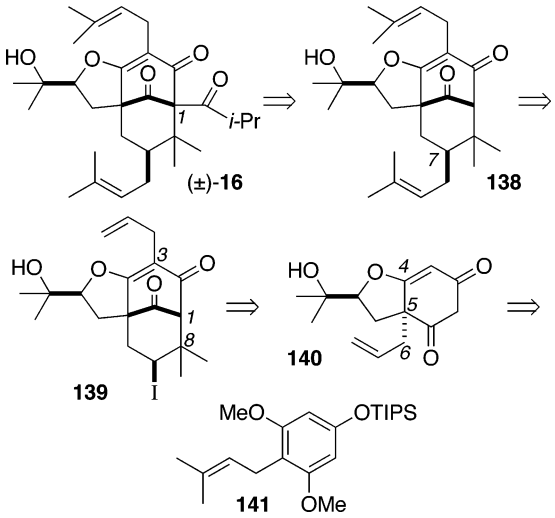


137 upon hydrolysis with H_2SO_4. The TBDPS group of **137** was removed, and the C(4) ketone was protected as the cyclic methyl acetal. Treatment with excess *m*-CPBA then promoted a regioselective Baeyer−Villiger reaction of the cyclobutanone to give the desired model lactone **124** in good yield.

5.2. Danishefsky's I-Mediated Electrophilic Cyclization Approach

Very recently, Danishefsky has described a total synthesis of garsubellin A that uses an electrophilic attack of a cyclohexanone on a prenyl group that is reminiscent of that described by Nicolaou.[85] In Danishefsky's retrosynthetic analysis (Scheme 8), the C(1) acyl group of (±)-**16** would be introduced by deprotonation of **138** and addition of isobutyraldehyde. The C(7) prenyl group of **138** would be introduced by free radical allylation of the iodide **139**. Removal of the C(3) allyl group of **139** and disconnection of the C(1)−C(8) bond by an iodocyclization reaction then led back to bicyclic **140**, which would be produced by dihydroxylation and alkylative dearomaticization of the phloroglucinol derivative **141**.

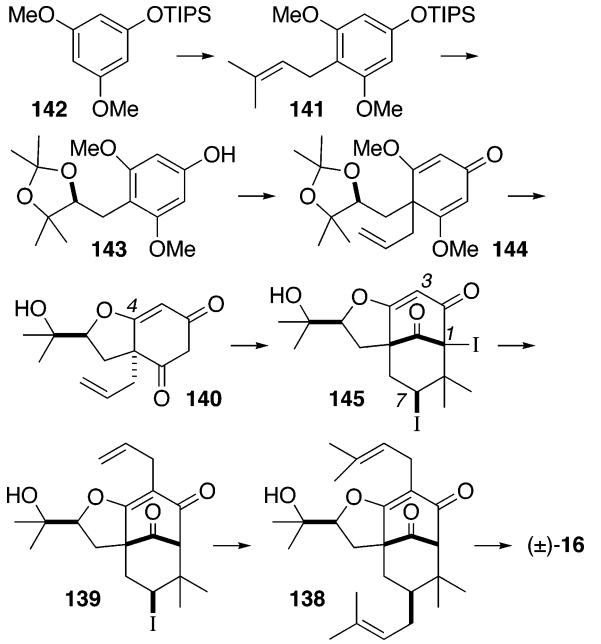
Scheme 8. Danishefsky's Retrosynthesis of Garsubellin A



The Danishefsky synthesis of **16** began by deprotonation of **142** and addition of prenyl bromide to give **141** (Scheme 9). Os-catalyzed dihydroxylation of **141** was followed by acetonide formation and removal of the TIPS group to give racemic **143**. Compound **143** was treated with allyl methyl carbonate in the presence of $Pd(OAc)_2$, Ph_3P, and Ti(O-*i*-Pr)$_4$, providing key dearomatized intermediate **144**, either by direct C-allylation or by O-allylation followed by a Pd-catalyzed Claisen rearrangement. Acidic hydrolysis of **144** removed the acetonide group and promoted conjugate addition of the nascent secondary alcohol to the ring to give a bicyclic acetal, forming the key O−C(4) bond; as the reaction mixture was allowed to age, elimination of MeOH from the acetal and hydrolysis of the other methyl enol ether eventually provided **140** as a single diastereomer.

The allyl group of **140** was subject to Grubbs cross-metathesis with 2-methyl-2-butene to convert it into a prenyl group, and, in a step reminiscent of Nicolaou's original approach, iodocyclization then provided the tricyclic diiodide **145**. Compound **145** was iodinated once again, at C(3), and halogen−metal exchange followed by treatment with allyl bromide not only introduced the allyl group at C(3) but also

Scheme 9. Danishefsky's Synthesis of Garsubellin A



promoted Wurtz-like coupling of C(1) and C(7)! Fortunately, this cyclopropanation step was easily reversed by addition of TMSI, affording **139**. Iodide **139** was subject to free radical allylation with allyltributyltin, installing the allyl group selectively in the sterically less hindered exo position, and another Grubbs cross-metathesis with 2-methyl-2-butene provided the diprenylated compound **138**. Finally, formation of the bridgehead silyl enol ether of **138**, iodination to give the bridgehead iodide, halogen−metal exchange, addition of isobutyraldehyde, and oxidation of the alcohol gave **16**.

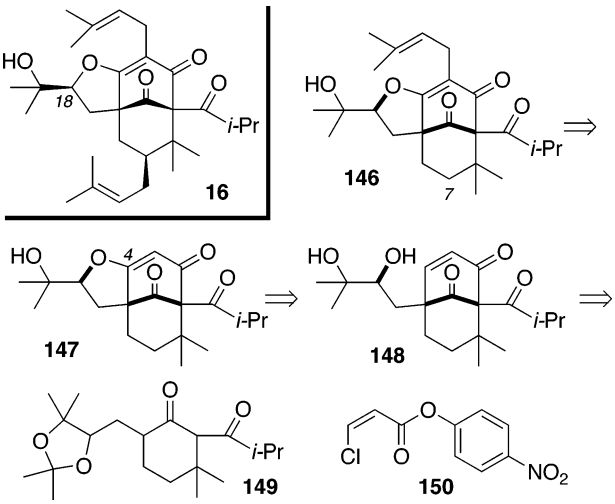
The Danishefsky synthesis is direct and efficient, and it relies on few protecting groups. The use of the diverse reactivity of I to introduce the C(1)−C(8) bond and the C(3), C(7), and C(1) substituents by electrophilic cyclization, transition-metal-catalyzed cross-coupling, radical substitution, and halogen−metal exchange, respectively, is particularly creative. Future work is needed to improve the introduction of the C(1) acyl group, which proceeds in fairly poor and variable yield, to prepare **143** in enantiopure form, and to extend this methodology to the synthesis of other PPAPs such as hyperforin.

5.3. Shibasaki's Addition–Elimination–Aldol Approach

Shibasaki's group chose as their model compound 7-deprenylgarsubellin A, **146** (Scheme 10), which has all of the features of garsubellin A (**16**) except the prenyl group attached to C(7).[87] Their plan was to introduce the C(3) prenyl group in the last step via a Stille coupling reaction between tributylprenyltin and the iodide prepared from β-alkoxy lactone **147**. The C(4)−O bond of **147** would be constructed via an intramolecular Wacker-type reaction of enone **148**. The bicyclo[3.3.1]nonane core of enone **148** was to be constructed by a stereospecific addition−elimination reaction between 1,3-diketone **149** and α,β-unsaturated ester **150** followed by a Dieckmann reaction. As will be discussed shortly, this key step failed to work as planned, and considerable synthetic effort was required to arrive at **148**.

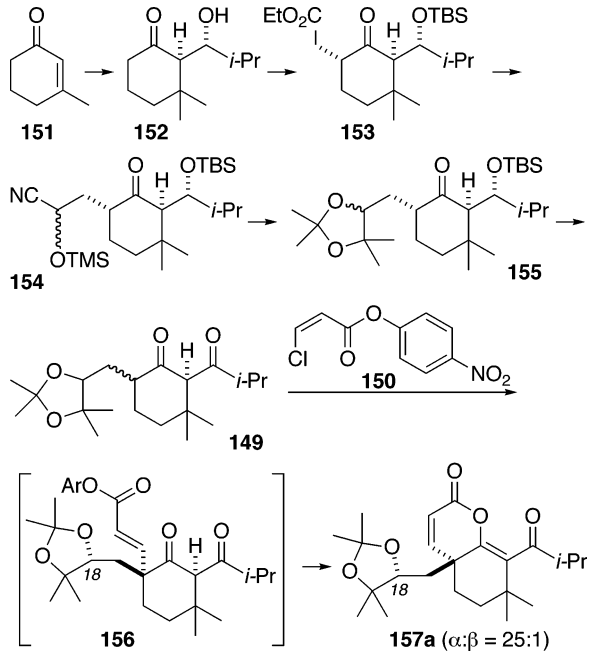
The synthesis began with conjugate addition of MeMgBr to α,β-unsaturated ketone **151** followed by trapping of the

Scheme 10. Shibasaki's Retrosynthesis of Garsubellin A



enolate with isobutyraldehyde to give **152** as a single stereoisomer (Scheme 11).[87] The OH group of **152** was protected, and the product was alkylated with ethyl bromoacetate to give **153** as a single trans isomer. Partial reduction of **153** with DIBAL and cyanosilylation of the aldehyde afforded **154** as an inconsequential 1.3:1 mixture of diastereomers. Addition of a higher order methylcuprate reagent to **154** gave a methyl ketone, which was further subjected to methylation and protection to give the acetonide **155**. Removal of the TBS group with $BF_3{\cdot}Et_2O$ and oxidation of the resulting secondary alcohol with Dess−Martin periodinane gave key intermediate **149** as an inconsequential 1.3:1 mixture of diastereomers. Unfortunately, the addition−elimination reaction between 1,3-diketone **149** and *cis*-β-chloroacrylate **150** failed to proceed as desired. The authors expected that addition−elimination would occur with retention of configuration about the electrophilic π bond and that a Dieckmann condensation would then give **148** (protected as the acetonide). Instead, the major product was the trans acrylate **156**. The authors found that **156** could be converted into **157** in the presence of *p*-nitrophenol and base. Extensive

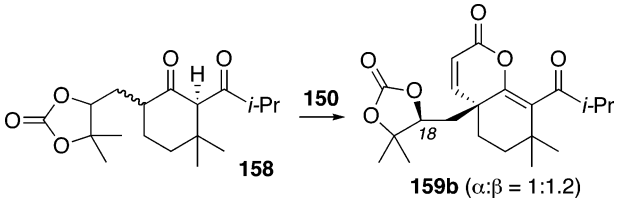
Scheme 11. Shibasaki's Approach to Garsubellin A, Part 1



optimization finally revealed conditions under which **149** could be directly converted to **157** in good yield. Unfortunately again, by far the major diastereomer produced under these conditions was the undesired **157a**.

Later, the Shibasaki group found that the carbonate **158** gave a much less diastereoselective addition−elimination reaction than the acetonide **149** did, affording larger quantities of the desired epimer **159b** (Scheme 12).[86]

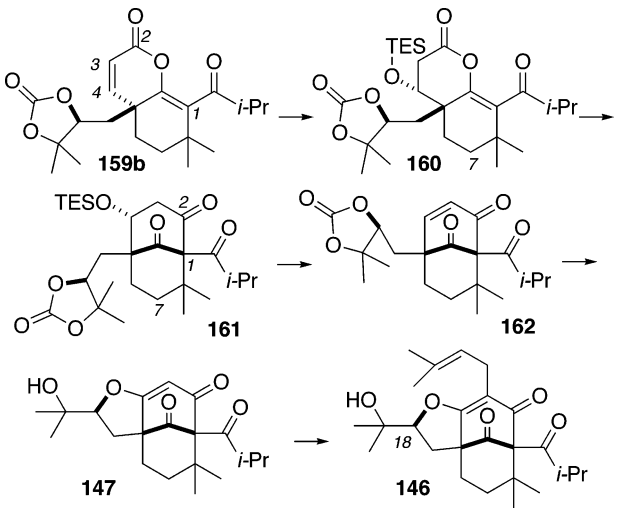
Scheme 12. Shibasaki's Approach to Garsubellin A, Part 2



It was necessary to remove the C(3−4) unsaturation of **159b** before the compound could be induced to form the C(1−2) bond (Scheme 13). Conjugate addition of an aminosilylcuprate to α,β-unsaturated lactone **159b** and immediate Tamao−Fleming oxidation with *m*-CPBA afforded a β-hydroxy lactone, which was protected with a TES group to give **160** in modest yield over the three steps.[86] In the preparation of the substrate for an aldol condensation, the lactone ring of **160** was opened with Me_2AlSEt to give the corresponding thioester, Fukuyama reduction of the thioester gave an aldehyde, and the aldehyde underwent an aldol reaction upon treatment with Al_2O_3, with Dess−Martin periodinane treatment affording triketone **161**. From this point, the sequence of reactions went as planned in the retrosynthetic analysis. Thus, **161** was converted to enone **162** by DBU-promoted β-elimination of TESOH. Deprotection of the carbonate of **162** with LiOH was followed by Wacker oxidation to afford the β-alkoxy enone **147**. Treatment of **147** with I_2 and CAN afforded the vinyl iodide, and Stille coupling with tributylprenyltin catalyzed by $PdCl_2$(dppf) introduced the prenyl group on C(3) and completed the synthesis of **146**. The acetonide **157a** with the unnatural C(18) configuration was also carried on to the C(18) epimer of **146** via a similar sequence of reactions.[87]

Shibasaki later found that the aldol reaction leading from **160** to **161** failed when there was a prenyl group at C(7).[84] As a result, the group abandoned this approach to garsubellin A and developed a very different one that culminated successfully in a total synthesis (vide infra).

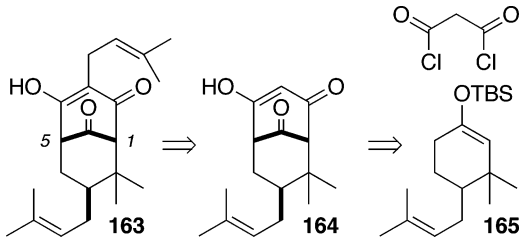
Scheme 13. Shibasaki's Approach to Garsubellin A, Part 3



5.4. Stoltz's Claisen–Dieckmann Approach

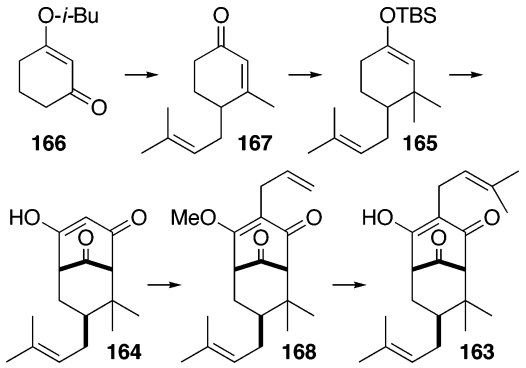
Stoltz's approach to the PPAPs had the advantage of producing a diprenylated bicyclic core in just 10 steps.[97] The retrosynthesis of model compound **163** began with disconnection of the C(3) prenyl group to give **164** (Scheme 13). The bicyclic core would then be introduced by a condensation reaction between silyl enol ether **165** (Scheme 14) and malonyl dichloride. This key step was based on a reaction reported by Effenberg in 1984,[98] in which 1-methoxy-1-cyclohexene reacted with malonyl dichloride to give a bicyclo[3.3.1]nonane-2,4,9-trione.

Scheme 14. Stoltz's Retrosynthesis of PPAPs



The synthesis of **163** began with α-prenylation of β-alkoxy enone **166** (Scheme 15). Addition of MeLi and acidic workup then gave α,β-unsaturated ketone **167**. Conjugate addition of dimethyl cuprate to **167** and subsequent addition of TBSCl provided the silyl enol ether **165**. Under optimal conditions, compound **165** underwent α,α′-annulation with malonyl dichloride to give the bicyclo[3.3.1]nonane-2,4,9-trione **164** as a single diastereomer in 36% yield. Unreacted enol ether was recovered in 59% yield as the keto form of **165**, which could be used again in the reaction sequence. Although the cyclization step proceeded only in modest yield, the steps prior to cyclization were relatively easy to execute and proceeded in excellent yields.

Scheme 15. Stoltz's Approach to Garsubellin A



The introduction of the C(3) prenyl group into **164** began by treatment with allyl alcohol under acidic conditions under a Dean−Stark trap. Thermal Claisen rearrangement followed by methylation with CH_2N_2 afforded the C-allylated β-alkoxy enone **168**. Finally, olefin cross-metathesis with 2-methyl-2-butene catalyzed by Grubbs' second-generation catalyst and subsequent saponification of the methyl ether with aqueous NaOH gave the final target model compound **163**.

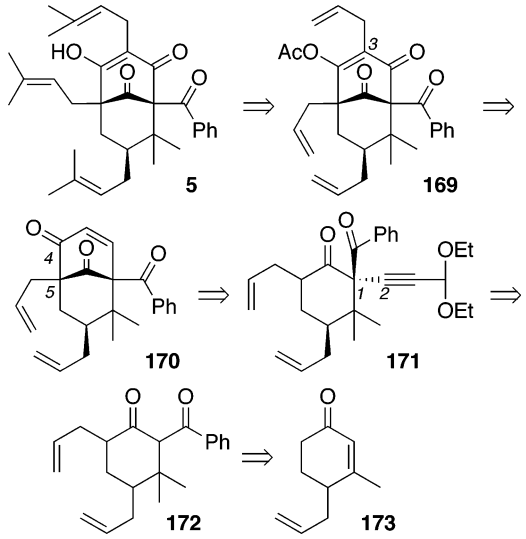
Stoltz tried to extend this methodology to analogues of **163** which would contain quaternary bridgehead C atoms, but most attempts failed, suggesting that the presence of

substituents at the α-positions of the masked ketone adversely affected the reactivity of the system. After prolonged experimentation, the group found rather arcane conditions (Cp_2HfCl_2, then KOH and $BnNEt_3Cl$) under which the methyl enol ether of 2,6-dimethylcyclohexanone would react with malonyl dichloride to give a bicyclo[3.3.1]nonane-2,4,9-trione. Unfortunately, the product was obtained only in 25% yield, proving indeed that substituted enol ethers are not good substrates for the Claisen−Dieckmann approach.

5.5. Grossman's Alkynylation–Aldol Approach

The Grossman group chose to focus its attention on nemorosone, **5**, because it had a simpler structure relative to other PPAPs such as garsubellin A and hyperforin.[99] The retrosynthetic analysis began with masking the sensitive prenyl groups as more robust allyl groups until the end of the synthesis, when they could be installed by Ru-catalyzed cross-metathesis of **169** with 2-methyl-2-butene (Scheme 16).

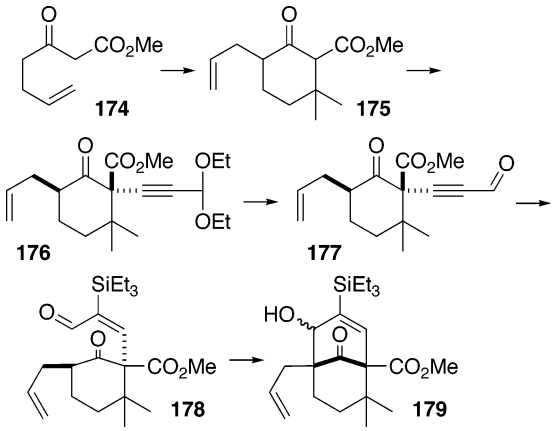
Scheme 16. Grossman's Retrosynthesis of Nemorosone



The C(3) allyl group of **169** would be installed by alkylation of the β-diketone group, which would in turn be installed by oxidation of enone **170**. The C(4)−C(5) bond of **170** would be formed by an intramolecular aldol reaction of a cis enal, which would be prepared by syn reduction and hydrolysis of the alkynyl acetal **171**. The C(1)−C(2) bond in **171** would be formed by alkynylation of β-diketone **172** with commercially available 3,3-diethoxypropyne, and **172** would be prepared by elaboration of cyclohexanone **173**. The alkynylation reaction to form the C(1)−C(2) bond was chosen because it was expected to be C-selective, because the small size of the alkynyl group was expected to make it easier to form the two contiguous quaternary centers in **171**, and because the alkynyl group was expected to be easily reduced to a cis enal, setting up the intramolecular aldol reaction and retaining functionality at C(2) to enable introduction of a ketone at that position.

The investigation began with a model study (Scheme 17). The dianion of β-keto ester **174** was prenylated in the presence of DMPU, and $SnCl_4$-catalyzed cyclization provided cyclic β-keto ester **175**. The β-keto ester **175** could be alkynylated in ca. 50% yield when $(EtO)_2CHC{\equiv}CSnBu_3$ was added to a mixture of **175** and Pb(OAc)4; the alkynylation failed when the free alkyne was used and when $Pb(OAc)_4$ was added to a mixture of the substrates. Acetal **176** was

Scheme 17. Grossman's Approach to Nemorosone

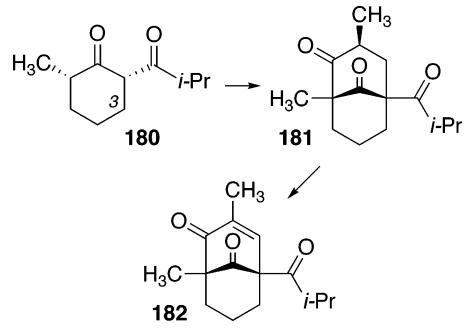


hydrolyzed to the corresponding ynal **177** in neat HCO_2H. Lindlar hydrogenation of **176** or **177** failed, but treatment of the $Co_2(CO)_6$ complex of **177** with excess Et_3SiH in the presence of $Me_3SiC{\equiv}CSiMe_3$ resulted in syn hydrosilylation, giving the (*E*)-α-silyl enal **178** in excellent yield with complete regio- and diastereoselectivity. The aldol reaction of **178** proceeded very easily in the presence of a catalytic amount of HCl, providing separable allylic alcohols **179** in 72% combined yield. The conversion of the allylic alcohol functionality of **179** to a β-diketone remained to be accomplished.

5.6. Nicolaou's Michael–Aldol Approach

In a recent publication which diverged dramatically from his previous approach, Nicolaou showed that 2-acylcyclohexanone **180** (and 2-acylcycloalkanones of other ring sizes) underwent a TfOH-catalyzed tandem Michael−aldol reaction with methacrolein (Scheme 18).[90] Oxidation of the aldol product with Dess−Martin periodinane then afforded bicyclic triketone **181**, and desaturation of **181** to give **182** was easily accomplished by selenation and oxidation. This strategy had the advantage of forming the two quaternary centers in just one step in relatively good yield from a simple cyclic ketone and aldehyde, but it remained to be seen whether the Michael reaction would proceed as readily when there was a quaternary center at C(3) of **180**. Also, as in Grossman's work, conversion of the enone functionality of **182** to a β-diketone remained to be accomplished.

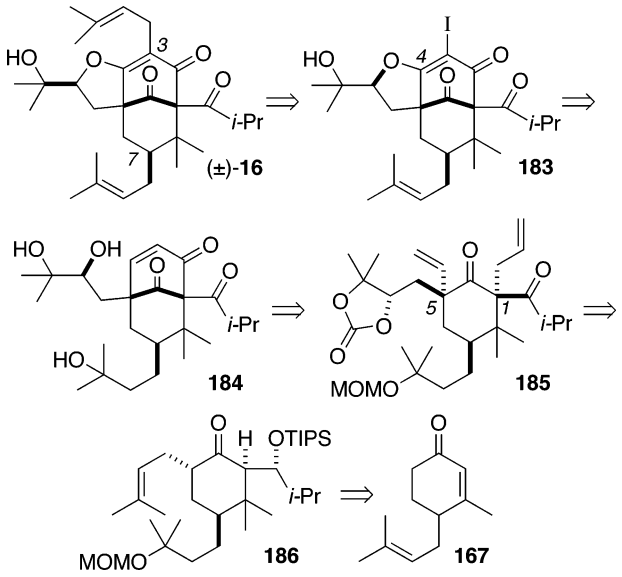
Scheme 18. Nicolaou's Michael−Aldol Approach to PPAPs



5.7. Shibasaki's Ring-Closing Metathesis Approach

Shibasaki's group very recently completed a total synthesis of racemic garsubellin A that utilized an approach completely different from that of his earlier synthetic ventures.[84] Discon-

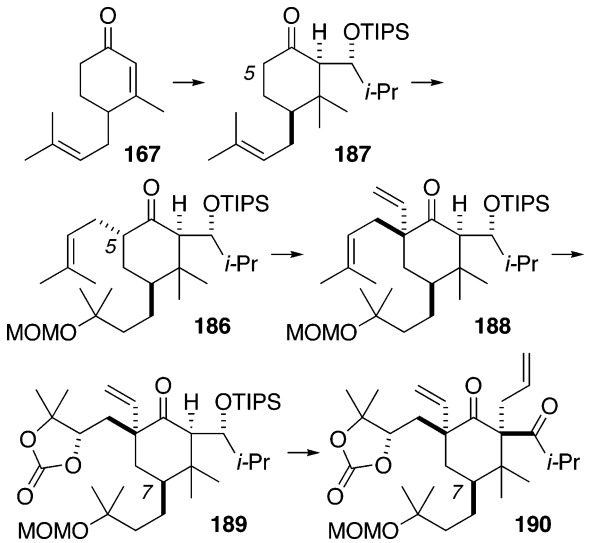
Scheme 19. Shibasaki's Ring-Closing MetathesisApproach to Garsubellin A



nection of the C(3) prenyl group of (±)-**16** gave **183**, the O−C(4) bond of which was expected to be formed by an intramolecular Wacker oxidation, as precedented in the group's earlier studies,[86] leading back to enone **184** (Scheme 19). Because their previous intramolecular aldol route failed when a C(7) prenyl group was present, the authors decided to introduce the enone bridge of **184** by ring-closing metathesis of the very congested α-vinyl α′-allyl cyclohexanone **185**. The key C(1) and C(5) quaternary centers of **185** were introduced into simpler ketone **186** by an aldol reaction and dehydration (vinyl group) and by an O-allylation and Claisen rearrangement (allyl group). The ketone **186** would be elaborated from simple enone **167**, an early intermediate in Stoltz's studies (Scheme 15).[97]

Copper-catalyzed conjugate addition of MeMgBr to **167**, trapping of the enolate with isobutyraldehyde, and protection of the resulting OH group with a TIPS group provided ketone **187** (Scheme 20). The prenyl group of **187** was hydrated and protected with a MOM group, and the ketone was then alkylated at the less hindered α-position, C(5), with prenyl bromide to give ketone **186**. Another deprotonation of **186**,

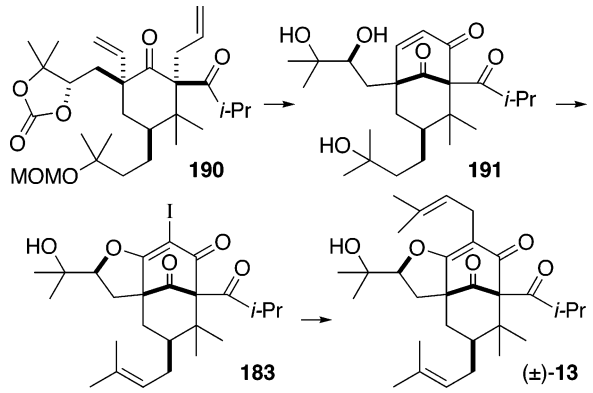
Scheme 20. Shibasaki's Synthesis of Garsubellin A, Part 1



again at C(5), was followed by another aldol reaction, this time with acetaldehyde; this reaction proceeded in surprisingly good yield, despite the tendency of sterically crowded aldols to fragment by a retro-aldol reaction. Dehydration of the aldol with Martin sulfurane then gave the α-vinyl ketone **188**. The prenyl group was then subject to Sharpless dihydroxylation with AD-mix-α, which provided the diol with zero diastereoselectivity. (AD-mix-β gave no product at all.) Formation of the carbonate and separation of the diastereomers gave **189**. The TIPS group of **189** was removed, the aldol was oxidized to the β-diketone, the ring O was allylated with allyl iodide, and a Claisen rearrangement on the face opposite the C(7) prenyl group provided fully quaternized diketone **190** with very high diastereoselectivity.

Ring-closing metathesis of **190** proceeded smoothly, as it always seems to do, with the Hoveyda−Grubbs catalyst, and the resulting alkene was oxidized in the allylic position with $(PhSe)_2$ and $PhIO_2$. Both protecting groups were then removed to give **191** (Scheme 21). The alcohol and enone moieties were then condensed oxidatively in the intramolecular Wacker oxidation that worked so well in Shibasaki's earlier work, and C(3) iodination and acid-catalyzed dehydration of the tertiary alcohol gave **183**. Finally, Stille coupling of **183** with prenyltributyltin afforded the target, (±)-**16**, in a total of 21 steps from **167**.

Scheme 21. Shibasaki's Synthesis of Garsubellin A, Part 2



Shibasaki also showed that alkylation of the Li enolate of 2-cyclohexenone with prenyl bromide in the presence of catalytic amounts of chiral tetraamine **192** (Figure 21), a previously unpublished compound from the Koga group, gave 6-prenyl-2-cyclohexenone with 95% enantiomeric excess in 65% yield. This compound could then be converted to enantioenriched **167** by the addition of MeLi and PCC oxidation.

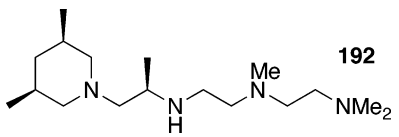


Figure 21. Chiral amine catalyst for asymmetric prenylation of 2-cyclohexenone.

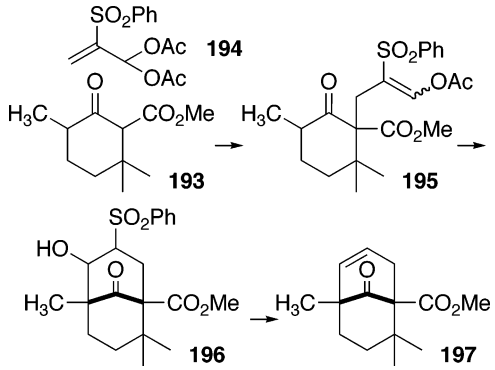
Shibasaki's synthesis of garsubellin A is an important milestone, but it has some deficiencies that will need to be addressed in future work aimed at this and other PPAPs. Most seriously, the dihydroxylation of **188** proceeds with no diastereoselectivity. Also, the oxidation of the C(2−4) enone of **191** to the β-alkoxy enone of **183** in the intra-

molecular Wacker oxidation relies on an internal OH group that is poised to attack the enone−Pd complex in intramolecular fashion. Although this method is perfectly suitable for PPAPs with a tetrahydrofuran ring fused to the C(4,5) bond, such as garsubellin A, it is much less so for PPAPs (such as hyperforin, **5**) that lack this feature. It remains to be seen how oxidation of the C(2−4) enone can be accomplished in syntheses of other PPAPs.

5.8. Kraus's Addition–Elimination–Addition Approach

Kraus found that β-keto ester **193** and diacetoxy vinyl sulfone **194** underwent a base-promoted addition−elimination reaction to give **195** (Scheme 22).[89] Transesterification of the acetate of **195** to the pivalate was followed by another base-promoted addition reaction to give bicyclic keto ester **196**, and acetylation of **196** followed by treatment with sodium amalgam gave alkene **197**. This method had the virtue of producing quaternary centers at both bridgehead C atoms of **197**, but further functionalization of the alkene was not demonstrated.

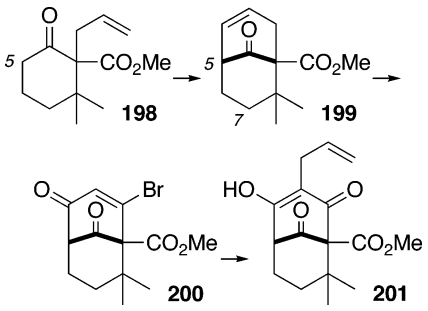
Scheme 22. Kraus's Addition−Elimination−Addition Approach to PPAPs



5.9. Kraus's Mn-Mediated Oxidative Free Radical Cyclization Approach

In an earlier approach to the synthesis of PPAPs, Kraus utilized a Mn(III)-based oxidative free radical cyclization of unsaturated β-keto ester **198** (itself prepared in three steps) to give bicyclic keto ester **199** (Scheme 23).[100] Treatment of **199** with 3.5 equiv of NBS followed by hydrolysis afforded β-bromo enone **200** as a single regioisomer. Substitution of the bromide with an allyloxy group followed by a Claisen rearrangement then gave **201**. The discovery of conditions that allowed full oxidation of the alkene of **199** to the β-bromo enone of **200** was a significant accomplishment, but the free radical bromination might not be applicable to a more substituted analogue of **199**, especially one with pendant allyl or prenyl groups at C(5) and C(7).

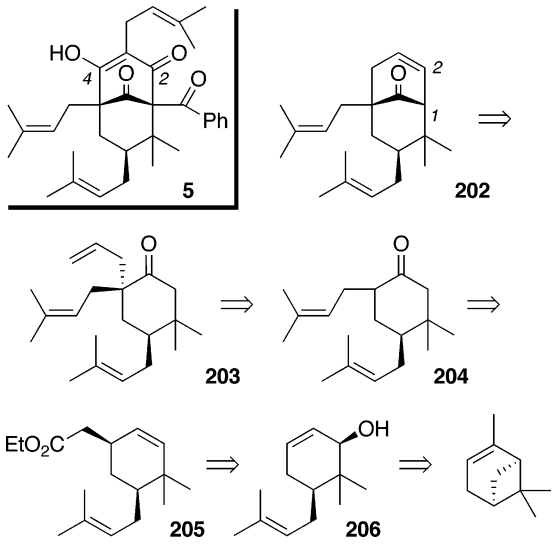
Scheme 23. Kraus's Oxidative Free Radical Cyclization Approach to PPAPs



5.10. Mehta's Pd-Mediated Oxidative Cyclization Approach

The first enantioselective approach to a PPAP was revealed by Mehta, who used (−)-α-pinene as the starting material.[94] Compound **202** (Scheme 24) was chosen as a model for nemorosone (**5**). In a strategy similar to that of Kraus, alkene **202** was disconnected at the C(1)−C(2) bond to give the monocyclic, diprenylated 2-acylcyclohexanone **203**. Removal of the α-allyl and -acyl groups from **203** gave the diprenyl cyclohexanone **204**, which would be prepared by elaboration of ester **205**. Ester **205** would be prepared from transposed cyclohexenol **206**, which would be prepared ultimately from (−)-α-pinene.

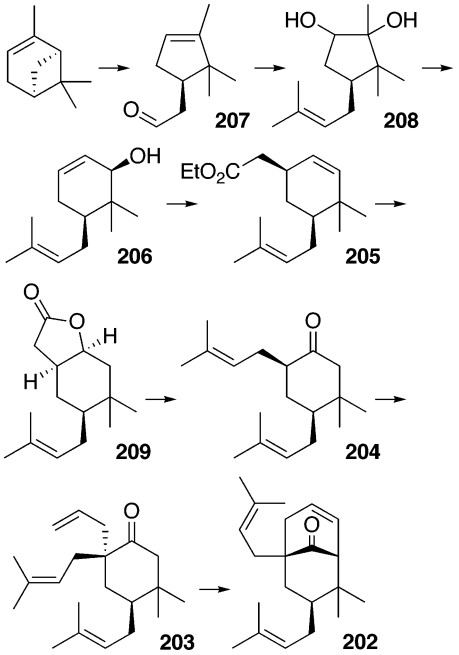
Scheme 24. Mehta's Retrosynthesis of PPAPs



Inexpensive α-pinene was stereoselectively epoxidized and the product fragmented upon addition of $ZnBr_2$ to give campholenic aldehyde **207** (Scheme 25).[101] OsO_4-catalyzed dihydroxylation of **207** and Wittig reaction of the aldehyde group with $Ph_3P{=}CMe_2$ gave the prenylated diol **208**. Oxidative cleavage of **208** with sodium periodate gave a keto aldehyde, which underwent intramolecular aldol cyclization to give an enone. A Luche reduction of the ketone occurred from the face opposite the prenyl group, producing allylic alcohol **206** with high selectivity. Compound **206** then underwent a stereospecific ortho ester Claisen rearrangement to provide ester **205**. Hydrolysis of **205**, iodolactonization, and reductive deiodination with Bu_3SnH gave lactone **209**. Reduction of the lactone to the lactol and a second Wittig reaction introduced the second prenyl group in moderate yield, and oxidation of the alcohol provided cyclohexanone **204**. The thermodynamic enolate of ketone **204** was formed with NaH, and alkylation with allyl bromide occurred exclusively from the kinetically favored axial direction to give triene **203** stereoselectively. In the key step, ketone **203** was converted to its silyl enol ether, and oxidative cyclization promoted by $Pd(OAc)_2$ gave the bicyclic compound **202** in modest yield.

The synthesis of **202** is the first enantiospecific synthesis of a PPAP-like compound, but it is not clear yet if the methodology can be applied to a more functionalized system.

Scheme 25. Mehta's Approach to PPAPs

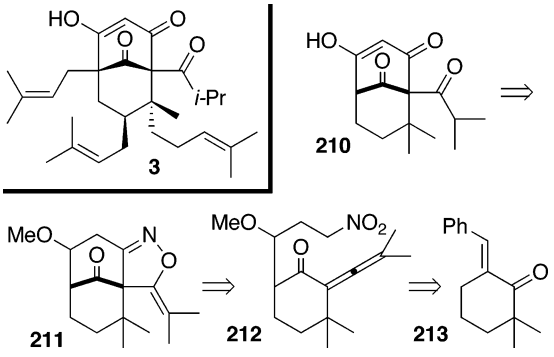


Moreover, Mehta's route to enantiopure **204** was quite lengthy, and a more expeditious route to this rather simple compound might be possible.

5.11. Young's Intramolecular Allene–Nitrile Oxide Cycloaddition Approach

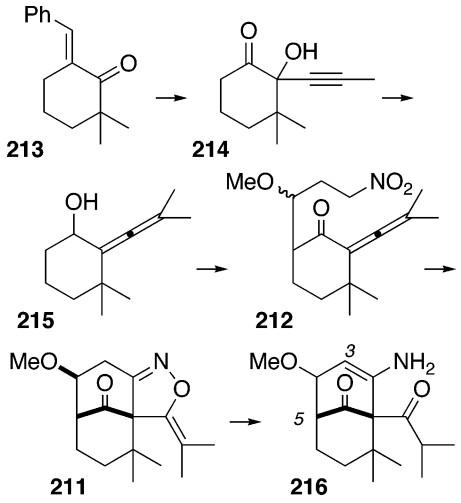
Young described an ingenious approach to the type A PPAP hyperevolutin A (**3**)[44] that was radically different from all others to date (Scheme 26).[92] Young realized that the nonenolizable β,β'-triketone group of model compound **210** could be derived from alkylidene isoxazole **211**, and **211** could in turn be prepared from **212** by an intramolecular nitrile oxide−allene cycloaddition. The allenic ketone **212** would be prepared from alkylidene cyclohexanone **213**.

Scheme 26. Young's Retrosynthesis of PPAPs



Addition of propynylmagnesium bromide to **213** and ozonolysis of the double bond gave α-hydroxyketone **214** (Scheme 27). Reduction of **214** with $LiAlH_4$ gave a 1,2-diol (as a mixture of diastereomers), which was further converted to the carbonate after treatment with carbonyl diimidazole. Conjugate addition of dimethyl cuprate to this propargyl carbonate then provided allenic alcohol **215**. The alcohol **215** was oxidized to the ketone and converted to the silyl enol ether, and a $TiCl_4$-promoted aldol condensation between this compound and the dimethyl acetal of 3-nitropropanal afforded nitro compound **212** as a mixture of diastereomers.

Scheme 27. Young's Approach to PPAPs



The key step of the synthesis, the intramolecular nitrile oxide−allene cycloaddition, occurred after the addition of phenyl isocyanate and Et_3N to **212** to give bicyclic adduct **211** in 40% yield and as a single diastereomer. The diastereomer of **212** that would have led to the diastereomer of **211** was apparently resistant to the intramolecular nitrile oxide−allene cycloaddition. Reductive cleavage of the isoxazoline ring with methanolic Raney nickel afforded primary enamine **216**, which had most of the features of the PPAPs. The isolation of **216** as a primary enamine in the absence of conjugative stabilization was a testament to the strong preference of C(3) to be sp^2-hybridized. The main drawback of this approach was the lack of a substituent at C(5) of **216**. On the other hand, the route was quite short and did not rely on carbonyl condensation reactions to form the key bonds.

6. Conclusion

The plant family Guttiferae comprises a large number of widely distributed species. The antidepressant activity of *Hypericum perforatum*, a member of the Guttiferae family, has generated much interest in the metabolites from this family. Over 100 biologically active polycyclic polyprenylated acylphloroglucinols (PPAPs) in either or both enantiomeric forms have been isolated from Guttiferae plants in the past few decades. These compounds share a highly oxygenated and densely substituted bicyclo[3.3.1]nonane-2,4,6-trione core adorned with prenyl or geranyl side chains. PPAPs exhibit a wide variety of biological activities such as antimicrobial, antidepressant, antioxidant, cytotoxic, and anti-HIV activities.

This paper represents the first review of the structure and chemical synthesis of PPAPs. The synthesis of these complex and fascinating chemical structures of PPAPs continue to be a challenging task for chemists. Although much progress has been made in recent years, many challenges remain, especially among the type B PPAPs, for which no synthesis has yet been reported.

7. References

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