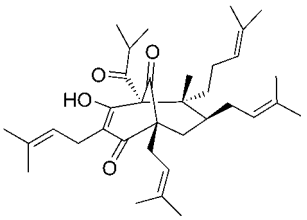
Ring Systems

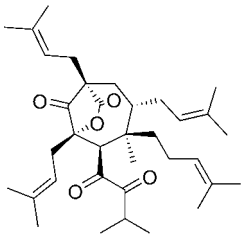
Construction of Highly Functionalized Medium-Sized Rings: Synthesis of Hyperforin and Perforatumone Model Systems**

K. C. Nicolaou, Giacomo E. A. Carenzi, and Valer Jeso*

Hyperforin[1] (**1**) and perforatumone[2] (**2**) are two secondary metabolites with unique molecular architectures and were



1: hyperforin



2: perforatumone

isolated from *Hypericum perforatum* (St. John's wort),[3] famous for its antidepressant properties. Despite their relatively small size, these structures constitute thorny synthetic challenges and remain to this day defiant to chemical synthesis.[4] As part of our efforts to develop synthetic routes to these and other natural and designed polyprenylated phloroglucinol derivatives, we sought a general method of entry into bridged medium-sized rings reminiscent of this class of compounds. Herein we report a novel synthetic sequence to such polyfunctional systems from simple cyclic ketones that involves a series of cascade reactions and delivers model systems of both hyperforin and perforatumone in a stereoselective manner.

Scheme 1 depicts the hypothetical strategy devised for reaching bridged medium (and potentially large)-sized rings of type **III**, **IV**, and **V** from simple building blocks such as disubstituted cyclic ketones **I** and α,β-unsaturated aldehydes **II**. Implementation of this strategy would require annulation of cyclic ketone **I** with the α,β-unsaturated aldehyde **II** to

[*] Prof. Dr. K. C. Nicolaou, Dr. G. E. A. Carenzi, V. Jeso
Department of Chemistry and
The Skaggs Institute for Chemical Biology
The Scripps Research Institute
10550 North Torrey Pines Road, La Jolla, California 92037 (USA)
Fax: (+1) 858-784-2469
E-mail: kcn@scripps.edu
and
Department of Chemistry and Biochemistry
University of California, San Diego
9500 Gilman Drive, La Jolla, California 92093 (USA)

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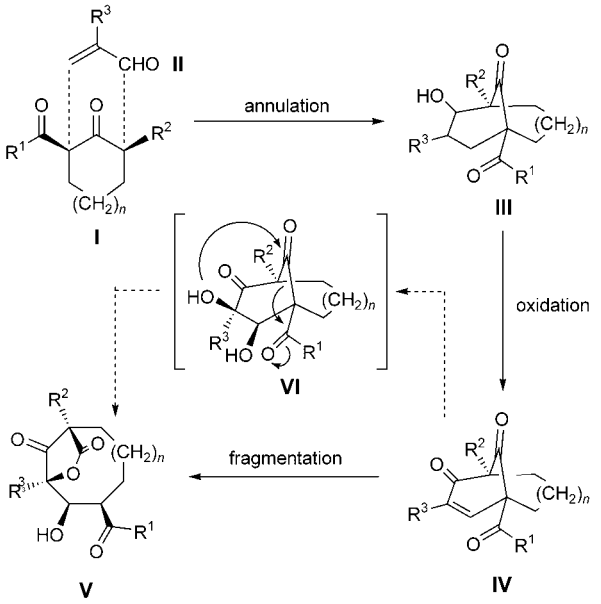
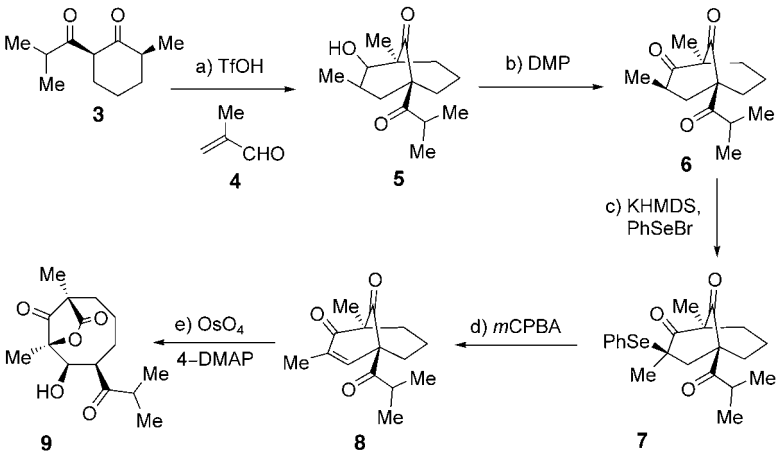


Scheme 1. General strategy for the construction of polyfunctional, bridged medium-sized rings **III**, **IV**, and **V**.

afford the bridged bicyclic system **III**, followed by oxidation of the latter compound to the α,β-unsaturated enone **IV**. Dihydroxylation and subsequent fragmentation of **IV** was expected to afford the ring-expanded product **V** via intermediate **VI**. Notably, besides the two-carbon expansion involved in the fragmentation reaction (**VI**→**V**), this process would concurrently form a new bridge, which being a lactone, can be conveniently disassembled to afford further multifunctional products. Noteworthy is also the choice of annulation partners **I** and **II** in which the fine-tuning of the reactivity of each compound at its two reactive ends was deemed crucial to the success of the anticipated cascade reaction to afford **III**. Favoring the proposed fragmentation was the proximity of the attending hydroxy group to the attached bridging carbonyl moiety, the closeness of its trajectory to the Bürgi–Dunitz angle,[5] and the strain released upon the event.

Delightfully, implementation of this plan with cyclohexanone derivative **3** and 2-methylacrolein (**4**) as starting materials proved successful (Scheme 2). Thus, mixing of diketone **3**[6] with acrolein **4** in CH_2Cl_2, followed by addition of TfOH[7] at −78 °C and slowly allowing the reaction mixture to reach ambient temperature, led to the formation of bicyclic hydroxy diketone **5** in 63% yield, presumably through: 1) initial activation (enolization) of the carbon atom between the two carbonyl groups of the cyclic diketone **3**, followed by 2) intermolecular 1,4-addition to the α,β-unsaturated aldehyde **4**, 3) protonation, and 4) intramolecular aldol reaction.[8] This annulation process is remarkable, not only for its efficiency, but also for its stereoselectivity: only two diastereomers of **5** (≈2:1) were obtained. Four diastereomers could plausibly be formed in this reaction, but the stereochemistry of the observed two was neither determined nor of consequence as both stereocenters were destroyed in the subsequent steps (see below). Continuing with the sequence (Scheme 1), the hydroxy group within the bicyclic product **5** (mixture of two compounds) was oxidized with DMP (81%) to afford tricarbonyl compound **6** (single compound), whose regioselective unsaturation (to afford enone **8** (Scheme 2)) proceeded smoothly through phenylselenide **7** (produced by sequential exposure to KHMDS and PhSeBr, 71%) by oxidation to the corresponding selenoxide with *m*CPBA (98%). Finally, stereoselective dihydroxylation of enone **8** from the *exo* face (OsO_4/4-DMAP) led conveniently to the targeted product **9** (Scheme 2; Table 3) in 68% yield, presumably through fragmentation[9] of the dihydroxy tricarbonyl compound corresponding to **VI** (Scheme 1) whose existence is apparently transient (not detected by TLC). While the resemblance of structures **5**–**8** to that of hyperforin (**1**) is obvious, the architecture of fragmentation product **9** contains one extra carbon in its medium-sized ring compared with that of perforatumone (**2**). Nevertheless, this sequence proved quite useful in synthesizing several other polyfunctional ring systems, including a bridged seven-membered ring corresponding to **2** (i.e. compound **25**, Table 2, Figure 1[10]).

The success of this process encouraged us to explore its optimization, generality, and scope. Table 1 lists the results of a number of experiments carried out to optimize the initial annulation procedure. Besides TfOH, a number of Lewis acids such as $Bi(OTf)_3$,[11] TMSOTf, $Sn(OTf)_2$, $Y(OTf)_3$, and AgOTf performed well, although it is not clear whether they act through the generation of TfOH. Optimizations for this step were also carried out for the five-membered (compound **10**, Table 2) and seven-membered rings (compound **11**, Table 2), as shown in Table 1. From these results we conclude



Scheme 2. Synthesis of polyfunctional ring systems. Reagents and conditions: a) TfOH (0.3 equiv), CH_2Cl_2, −78→25 °C, 1.5 h, 63%; b) DMP (1.5 equiv), py, CH_2Cl_2, 25 °C, 81%; c) KHMDS (1.15 equiv), THF, −41 °C, 2 h; then PhSeBr (1.4 equiv), −41 °C, 15 min, 71%; d) *m*CPBA (2.0 equiv), CH_2Cl_2, −10→0 °C, 30 min, 98%; e) OsO_4 (1.1 equiv), 4-DMAP (1.1 equiv), *t*BuOH/H_2O (1:1), 25 °C, 1 h, 68%. Tf = trifluoromethanesulfonyl; DMP = Dess–Martin periodinane; py = pyridine; KHMDS = potassium bis(trimethylsilyl)amide; *m*CPBA = *m*-chloroperbenzoic acid, 4-DMAP = 4-dimethylaminopyridine.

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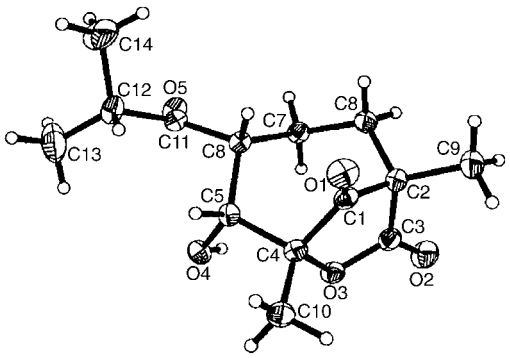


Figure 1. ORTEP drawing of **25** drawn at the 30% probability level.

that the best catalysts for this reaction can be found from the collection of TfOH, TMSOTf, and the triflate salts of Bi, Sn, Y, and Ag.

As shown in Table 2, the five- to ten-membered ring disubstituted ketones (**10**, **3**, **11**–**14**) entered and completed the sequence to the final lactone-bridged fragmentation products (**25**, **9**, **26**–**29**, respectively) via the corresponding intermediate compounds (**15**, **5**, **16**–**19**, and **20**, **8**, **21**–**24**) in varying yields. Thus, while the five- to eight-membered ring ketones performed well and yielded the seven- to ten-membered ring systems (Table 2, entries 1–4), the larger-ring ketones behaved erratically both in the initial (annulation) and in the final (fragmentation) steps to afford the expected products in low yields (Table 2, entries 5 and 6). The higher flexibility of the larger-ring substrates may be responsible for the poor performance of these ring-forming and -rupturing reactions, a hypothesis that was supported by the refusal of an open-chain disubstituted ketone (i.e. 2,4,6-trimethylheptan-3,5-dione) to enter the initial productive step (i.e. the annulation step).

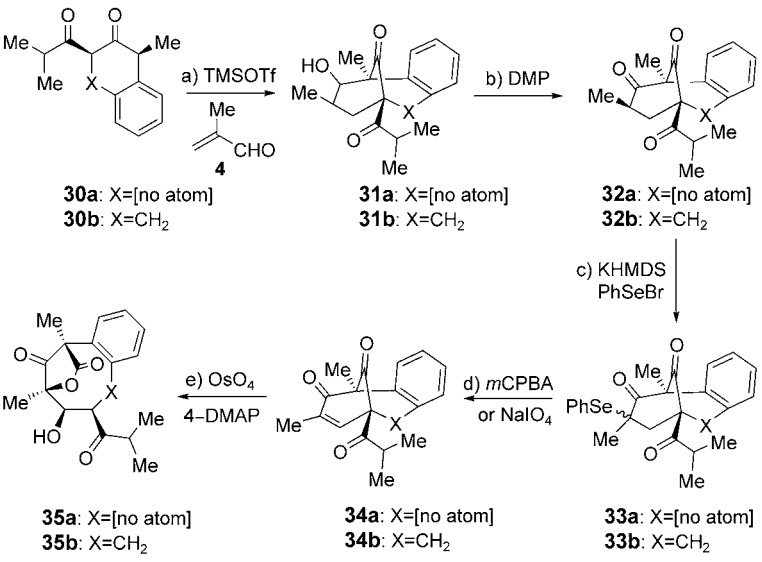
As a further demonstration of the generality of the developed synthesis of polyfunctional medium-sized rings, we attempted the construction of the fully substituted seven- and eight-membered bridged ring systems **31a,b**–**35a,b** (Scheme 3). Each carbon atom of these benzenoid fused ring systems is uniquely substituted, making them both synthetically challenging and potentially useful as biological probes. Thus, the substituted diketones **30a** and **30b** upon reaction with methyl acrolein (**4**) under the influence of TMSOTf, formed the annulated products **31a** (41%) and **31b** (31%), respectively. The latter compounds were then oxidized with DMP to the corresponding triketones **32a** (60%) and **32b** (61%), which were subjected to the phenylselenenylation/oxidation procedure to afford enones **34a** (74%) and **34b** (56%) via **33a** and **33b**. Finally, exposure of **34** to the OsO_4/4-DMAP conditions led directly to the targeted products **35a** (38%; Table 3) and **35b** (31%) through the postulated dihydroxylation/fragmentation cascade (yields unoptimized).

The described synthetic technology offers rapid and convenient build-up of molecular complexity from simple and readily available starting materials. Its application to the synthesis of natural and designed molecules containing medium-sized rings (seven- to ten-membered) appears particularly attractive and should be forthcoming.

Table 1: Optimization of annulation conditions (**I** + **II**→**III**)[a]

Entry	Substrate	Solvent	Equiv	*t* [h]	Product	Yield [%][b]
1	**3**	TfOH	0.3	1.5	**5**	63
2	**3**	$Bi(OTf)_3$	0.3	6	**5**	58
3	**3**	TMSOTf	0.5	1.5	**5**	65
4	**3**	$Sn(OTf)_2$	0.3	24	**5**	68
5	**3**	$Y(OTf)_3$	0.3	40	**5**	43
6	**3**	AgOTf	0.3	40	**5**	53
7	**3**	$CeCl_3$	0.3	24	**5**	0
8	**3**	Nafion	0.3	24	**5**	0
9	**10**	TfOH	0.3	3.5	**15**	33
10	**10**	$Bi(OTf)_3$	0.3	24	**15**	29
11	**10**	TMSOTf	0.5	3	**15**	46
12	**10**	$Sn(OTf)_2$	0.3	24	**15**	33
13	**10**	$Y(OTf)_3$	0.3	30	**15**	37
14	**10**	Nafion	1	24	**15**	0
15	**10**	Dowex	1	24	**15**	0
16	**10**	$Nd(OTf)_3$	0.3	24	**15**	trace
17	**10**	$Eu(OTf)_3$	0.3	24	**15**	trace
18	**10**	TfOH	0.3	24	**16**	56
19	**11**	$Bi(OTf)_3$	0.3	18	**16**	58
20	**11**	TMSOTf	0.5	3	**16**	47
21	**11**	$Sn(OTf)_2$	0.3	24	**16**	51
22	**11**	AgOTf	0.3	30	**16**	trace

[a] See Scheme 1 and Table 2. Reactions were carried out in CH_2Cl_2 at −78→25 °C on a 0.5-mmol scale. [b] Yields of chromatographically and spectroscopically homogeneous materials.



Scheme 3. Synthesis of fused benzenoid medium-sized ring systems **35a** and **35b**. Reagents and conditions: a) TMSOTf (0.5 equiv), CH_2Cl_2, −78→25 °C, 1.5 h, 41% (**31a**), 31% (**31b**); b) DMP (1.5 equiv), py (10 equiv), CH_2Cl_2, 25 °C, 3 h, 60% (**32a**), 61% (**32b**); c) KHMDS (1.15 equiv), THF, −41 °C, 2 h; then PhSeBr (1.4 equiv), −41 °C, 52% (**33a**), KHMDS (1.15 equiv), THF, −41 °C, 2 h; then PhSeBr (1.4 equiv), −78 °C, 50% (**33b**); d) *m*CPBA (2.0 equiv), CH_2Cl_2, −10→0 °C, 30 min, 74% (**34a**), $NaIO_4$ (10.0 equiv), $NaHCO_3$ (5.0 equiv), MeOH/H_2O (4:1), 0→25 °C, 56% (**34b**); e) OsO_4 (1.1 equiv), 4-DMAP (1.1 equiv), *t*BuOH/H_2O (1:1), 25 °C, 38% (**35a**) 31% (**35b**). TMS = trimethylsilyl.

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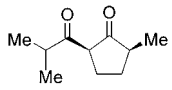
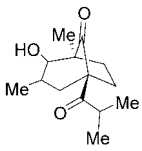
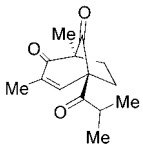
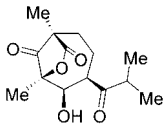
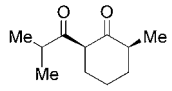
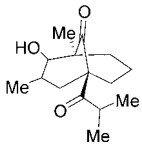
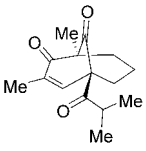
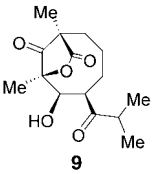
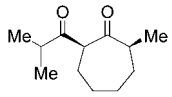
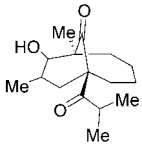
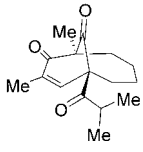
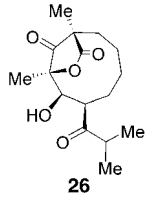
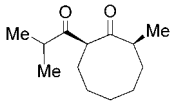
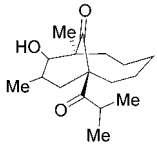
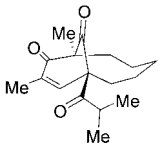
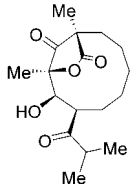
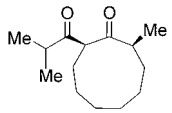
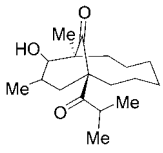
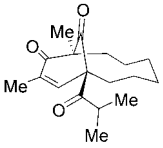
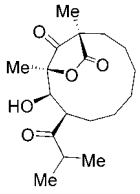
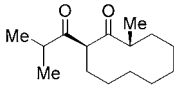
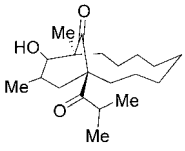
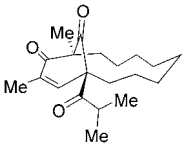
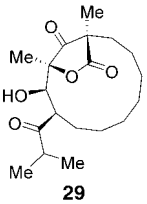
Table 2: Synthesis of highly functionalized medium ring systems by annulation-oxidation-fragmentation cascade[a]

Entry	Substrate	Annulation Product	Yield [%][b]	Oxidation Product	Yield [%][b,c]	Fragmentation Product	Yield [%][b]
1[d]	 **10**	 **15**	46	 **20**	37	 **25**	39
2[e]	 **3**	 **5**	68	 **8**	57	 **9**	68
3[f]	 **11**	 **16**	58	 **21**	38	 **26**	53
4[g]	 **12**	 **17**	30	 **22**	35	 **27**	56
5[d]	 **13**	 **18**	4[h]	 **23**	58	 **28**	21
6[d]	 **14**	 **19**	4[h]	 **24**	60	 **29**	27

[a] Reactions were carried out on a 0.1–5.0-mmol scale under the conditions specified in Scheme 2. [b] Yields of chromatographically and spectroscopically homogeneous materials. [c] Overall yield for the three steps from annulation product. [d] TMSOTf was used as a catalyst for the annulation step. [e] $Sn(OTf)_2$ was used as a catalyst for the annulation step. [f] $Bi(OTf)_3$ was used as a catalyst for the annulation step. [g] TfOH was used as a catalyst for the annulation step. [h] Yield estimated from the pure ketone obtained after oxidation with DMP (the annulation product was contaminated by inseparable oligomeric material).

Keywords: annulation · fragmentation · medium-sized rings · natural products · synthetic methods

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Table 3: Selected physical properties for compounds **8**, **9**, and **35a**.

8: $R_f = 0.48$ (silica gel, hexanes/EtOAc 7:3); IR (film): $\tilde{\nu}_{max} = 2978$, 2931, 1725, 1707, 1666, 1448, 1378, 1278, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.91$ (s, 1H), 2.89 (sept, $J = 6.6$ Hz, 1H), 2.35 (td, $J = 7.2$ Hz, 1H), 2.01–1.99 (m, 1H), 1.96 (s, 3H), 1.88–1.83 (m, 1H), 1.68–1.46 (m, 3H), 1.21 (s, 3H), 1.14 (d, $J = 6.6$ Hz, 3H), 1.11 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 212.4$, 207.9, 199.7, 140.3, 140.2, 66.4, 62.5, 41.7, 38.8, 32.5, 20.1, 19.9, 18.4, 16.2, 16.0 ppm; HRMS (FAB) (%): calcd for $C_{15}H_{20}O_3Na$ [M+Na^+]: 271.1305; found: 271.1304

9: $R_f = 0.18$ (silica gel, hexanes/EtOAc 7:3); IR (film): $\tilde{\nu}_{max} = 3459$, 2978, 2931, 1742, 1707, 1454, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 4.20$ (br s, 1H), 3.17–3.13 (m, 1H), 2.70 (sept, $J = 6.8$ Hz, 1H), 2.39–2.30 (m, 1H), 1.97–1.93 (m, 1H), 1.86–1.80 (m, 2H), 1.55 (s, 3H), 1.42–1.32 (m, 1H), 1.26 (s, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 1.02 ppm (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 217.2$, 216.8, 175.8, 91.9, 76.7, 51.1, 48.7, 39.7, 38.7, 23.1, 22.6, 22.4, 20.2, 19.7, 17.6 ppm; HRMS (FAB) (m/z): calcd for $C_{15}H_{23}O_5$ [M+H^+]: 283.1540; found: 283.1548

35a: $R_f = 0.11$ (silica gel, hexanes/EtOAc 7:3); IR (film): $\tilde{\nu}_{max} = 3434$, 2967, 2919, 1758, 1725, 1453, 1372, 1243, 1095, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.47$–7.32 (m, 3H), 7.07–7.00 (m, 1H), 5.06 (d, $J = 3.3$ Hz, 1H), 4.35 (d, $J = 3.3$ Hz, 1H), 2.72 (sept, $J = 6.8$ Hz, 1H), 1.89 (s, 3H), 1.40 (s, 3H), 1.19 (d, $J = 6.8$ Hz, 1H), 1.05 ppm (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.7$, 201.4, 168.9, 136.1, 132.0, 130.9, 130.0, 129.3, 126.3, 80.2, 73.0, 60.4, 58.3, 38.7, 22.7, 19.7, 19.6, 16.0 ppm; HRMS (FAB) (m/z): calcd for $C_{18}H_{21}O_5$ [M+H^+]: 317.1383; found: 317.1390

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