Cyclic Sesquiterpene–Flavanone [4+2] Hybrids, Syzygioblanes A–C, Found in an Indonesian Traditional Medicine, “Jampu Salo” (Syzygium oblanceolatum)

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Cyclic Sesquiterpene−Flavanone [4+2] Hybrids, Syzygioblanes A−C, Found in an Indonesian Traditional Medicine, "Jampu Salo" (*Syzygium oblanceolatum*)

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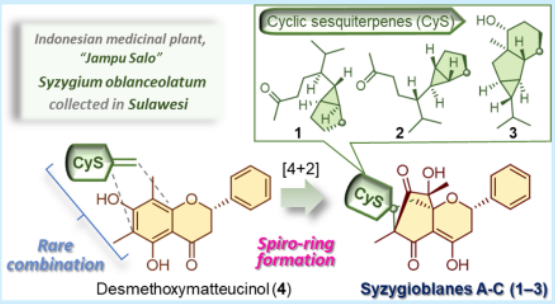
ABSTRACT: A plant used in an Indonesian traditional herbal medicine as a diabetes treatment and known locally as "Jampu Salo" was collected on Sulawesi Island, Indonesia. It was identified as *Syzygium oblanceolatum* (C. B. Rob.) Merr. (Myrtaceae) and found for the first time in Sulawesi; it was previously reported only in the eastern Philippines and Borneo. A phytochemical study of *S. oblanceolatum* led to the isolation of three unprecedented meroterpenoids, syzygioblanes A−C (**1**−**3**, respectively). These compounds might be biosynthesized through [4+2] cycloaddition of various germacrane-based cyclic sesquiterpenoids with the flavone desmethoxymatteucinol to form a spiro skeleton. The unique and complex structures were elucidated by microcrystal electron diffraction analysis in addition to general analytical techniques such as high-resolution mass spectrometry, various nuclear magnetic resonance methods, and infrared spectroscopy. Synchrotron X-ray diffraction and calculations of electronic circular dichroism spectra helped to determine the absolute configurations. The newly isolated compounds exhibited collateral sensitivity to more strongly inhibit the growth of a multidrug resistant tumor cell line compared to a chemosensitive tumor cell line.



"Jampu Salo" is the local name for a leaf decoction used in Indonesian traditional folk medicine to treat diabetes. The plant was collected on Sulawesi Island in 2018 and identified as *Syzygium oblanceolatum* by taxonomist Dr. Wuu-Kuang Soh. This report is the first record of *S. oblanceolatum* from Sulawesi, known previously only in the Eastern Philippines and Borneo.[1]

The plant genus *Syzygium*, distributed in subtropical to tropical regions, contains numerous species that contribute significantly to the diversity of tropical forests, especially in Southeast Asia. Its enormous morphological and ecological variations make phylogenetic elucidation difficult, although ~1200 species have been identified to date.[2] *Syzygium aromaticum* (L.) Merr. & L. M. Perry, the best-known species, is traditionally used in East Asia as a spice (clove) in cooking, as a treatment for burns and wounds, and as an analgesic in dentistry. *Syzygium jambos* (L.) Alston and *Syzygium fibrosum* (F. M. Bailey) T. G. Hartley & L. M. Perry are widely used as foods, such as jams and jellies, while *Syzygium cordatum* Hochst ex Krauss, *Syzygium samarangense* (Blume) Merr. & L. M. Perry, *S. aromaticum*, and *Syzygium cumini* (L.) Skeels are used to treat cancer, fever, diarrhea, and diabetes. Although the genus *Syzygium* has many medicinal properties and is used in traditional remedies, surprisingly few species have been evaluated phytochemically, and there are no phytochemical reports regarding *S. oblanceolatum*.

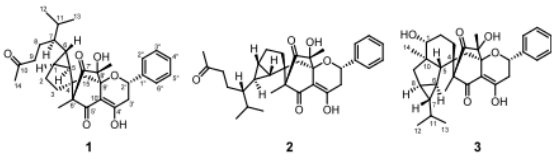


Figure 1. Structures of syzygioblanes A−C (**1**−**3**, respectively).

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Our phytochemical study of *S. oblanceolatum* resulted in the identification of three structurally and biologically unique meroterpenoids, syzygioblanes A−C (**1**−**3**, respectively),[3] which are hybrids of a germacrane-based cyclic sesquiterpene and a flavanone (Figure 1).

Compound **1** was obtained as a colorless amorphous solid with a molecular formula of $C_{32}H_{40}O_6$ established from a protonated molecule peak at m/z 521.2893 $[M + H]^+$ (calcd 521.2903) by HRMS. IR absorptions at 1717, 1663, and 1603 cm^{-1} implied the presence of carbonyl(s) and an α,β-unsaturated ketone. The ^1H NMR spectrum (Table 1) indicated the presence of a deshielded oxymethine [δ_H 5.20 (1H, dd)], five methyls [δ_H 0.91, 0.88 (each 3H, d), δ_H 1.43, 1.24 (each 3H, s)], including a deshielded methyl [δ_H 2.13 (3H, s)], a monosubstituted benzene [δ_H 7.40, 7.39 (each 2H, m), 7.34 (1H, m)], and a hydrogen-bonded hydroxy group (δ_H 12.6). The ^{13}C NMR spectrum suggested 32 carbons (Table 2); additional observation combined with DEPT135 and HMQC spectra assigned them as three ketone carbonyl carbons (δc 209.4, 208.6, 196.0), eight sp^2 carbons, including one oxygenated (δc 168.8) and six aromatic [δc 140.1, 128.7 (overlapped), 128.5, 126.5 (overlapped)], four quaternary carbons (δc 66.2, 49.8), including two oxygenated (δc 78.2, 76.4), six methines (δc 47.3, 32.0, 30.6, 24.8, 22.7), including an oxymethine (δc 73.8), six methylenes (δc 45.2, 42.6, 35.0, 31.5, 24.6, 23.6), and five methyls (δc 29.9, 22.3, 21.0, 17.9, 6.9). A $^1H-^1H$ COSY correlation of H-2′/H-3′, HMBC correlations from H-2′ to C-9′/C-1″/C-2″, H-3′ to C-4′/C-10′, and the protons of CH_3-6′ to C-5′/C-6′/C-7′ and CH_3-8′ to C-7′/C-8′/C-9′, and H2BC correlations between H-3″/C-2″ and H-4″/C-3″ implied that compound **1** has a 5,7-dioxo-6,8-dimethylflavanone skeleton (Figure 2).

Table 1. ^1H NMR Data for Compounds 1−3 (600 MHz, $CDCl_3$)

	δ_H		
position	1	2	3
1	0.97 m	1.18 m	3.16 dd (11.2, 4.4)
2	1.65 m	1.70 m	1.49 m, 1.56 m
3	0.94 m, 1.19 m	1.24 m, 1.72 m	1.15 m, 1.56 m
5	0.71 dd (6.3, 3.4)	0.97 dd (6.0, 3.4)	0.65 d (5.7)
6	0.56 ddd (10.0, 3.4, 3.2)	0.34 ddd (10.1, 3.4, 3.4)	0.56 m
7	0.41 m	0.50 m	0.49 m
8	1.41 m, 1.62 m	1.56 m, 1.65 m	1.10 m
9	2.37 m, 2.52 m	2.40 m, 2.52 m	0.75 m, 1.72 m
11	1.82 m	1.66 m	1.25 m
12	0.88 d (6.9)	0.93 d (6.9)	1.02 d (6.8)
13	0.91 d (6.9)	0.88 d (6.9)	0.83 d (6.8)
14	2.13 s	2.14 s	0.74 s
15	1.40 d (12.8), 2.55 d (12.8)	2.22 d (12.8), 2.67 d (12.8)	1.73 d (12.2), 2.28 d (12.2)
2′	5.20 dd (8.4, 4.1)	5.13 dd (8.6, 4.8)	5.29 dd (6.9, 4.4)
3′	2.69 m	2.61 m	2.77 m, 2.85 m
2″, 6″	7.39 m	7.39 m	7.44 m
3″, 5″	7.40 m	7.38 m	7.39 m
4″	7.34 m	7.34 m	7.35 m
4′-OH	12.6 brs	12.6 brs	12.9 brs
6′-Me	1.24 s	1.16 s	1.16 s
8′-Me	1.43 s	1.44 s	1.40 s
8′-OH			2.45 brs

Table 2. ^{13}C NMR Data for Compounds 1−3 (150 MHz, $CDCl_3$)

	δ_C		
position	1	2	3
1	22.7	28.0	77.6
2	24.6	28.8	27.8
3	31.5	35.7	33.4
4	66.2	68.5	68.8
5	32.0	34.4	56.5
6	24.8	22.8	24.3
7	47.3	46.9	48.8
8	23.6	25.5	23.0
9	42.6	42.1	44.2
10	209.4	209.2	60.0
11	30.6	31.3	30.3
12	21.0	19.5	21.6
13	17.9	19.3	20.9
14	29.9	30.0	16.4
15	45.2	44.5	37.9
2′	73.8	74.4	73.3
3′	35.0	36.3	34.0
4′	168.8	169.3	169.2
5′	196.0	196.2	194.3
6′	49.8	50.5	43.3
7′	208.6	208.4	207.6
8′	78.2	76.4	76.4
9′	76.4	77.8	77.6
10′	108.3	108.4	110.1
1″	140.1	140.2	140.2
2″, 6″	126.5	126.1	126.9
3″, 5″	128.7	128.8	128.7
4″	128.5	128.5	128.6
6′-Me	6.9	7.4	6.8
8′-Me	22.3	22.6	22.3

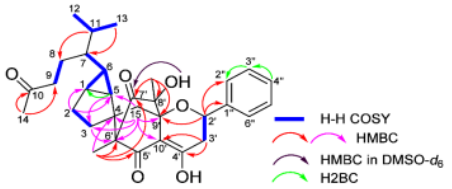

Figure 2. Key correlations of COSY, HMBC, and H2BC for **1**.

In addition, the presence of a cyclopentane was suggested by the HMBC cross peaks between H-2/C-1 and C-5 and H-5/C-3, as well as the $^1H-^1H$ COSY correlation of H-2/H-3. Furthermore, the H2BC correlation of H-5/C-1 in addition to the $^1H-^1H$ COSY correlations of H-1/H-6/H-5 indicated the presence of a cyclopropane, which was fused to the cyclopentane to form a bicyclic system, a bicyclo[3.1.0]hexane. Moreover, the HMBC correlations from H-15 to C-9′/C-10′/C-6′/C-3/C-4/C-5, H-3 to C-6′, and CH_3-6′ to C-4 indicated an unusual carbon−carbon framework containing a spiro[4.5]-decane (C-4 is the spirocarbon) and a bicyclo[2.2.2]octane (C-4 and C-15 are bridge carbons). The $^1H-^1H$ COSY correlations of H-6/H-7, H-8/H-9, and H-11/H-12 and H-13 and the HMBC correlations from H-13 to C-7, H-11 to C-8, and H-14 to C-10 and C-9 supported the presence of isopropyl and butanone fragments at C-7, which, in turn, was connected to C-6. These data indicated that compound **1** is a

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meroterpenoid, specifically a 6,8-dimethylflavonoid hybridized with a sesquiterpenoid. A hydroxy group at C-8′ was determined from an OH/C-7′ HMBC correlation measured in DMSO-d_6. This extremely unique skeleton was further verified by microcrystal electron diffraction (MicroED) analysis (Figure 3).[4] The relative configuration of **1** was

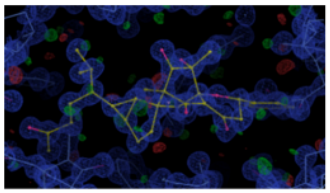

Figure 3. Structure of syzygioblane A (**1**) from MicroED CryoEM.

deduced from the combined NOESY correlations of H-1/H-5/H-7/H-9a/H-9b, H-6/CH_3-6′, and H-2′/CH_3-8′ (Figure 4),

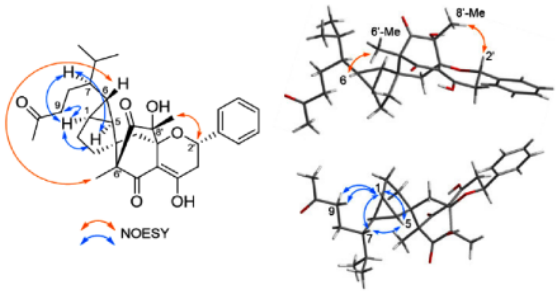

Figure 4. Key NOESY correlations for syzygioblane A (**1**).

as well as MicroED analysis. Additionally, synchrotron X-ray diffraction analysis with a Flack parameter of 0.07(5) (Figure 5) and ECD calculations (Figure 6) established the absolute configuration of **1** (syzygioblane A).

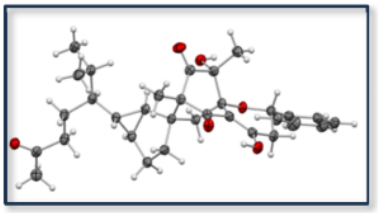

Figure 5. ORTEP view of syzygioblane A (**1**) showing a 50% probability thermal motion ellipsoid.

Compound **2** was isolated as a colorless, amorphous solid. Compounds **1** and **2** have the same molecular formula ($C_{32}H_{40}O_6$) based on a protonated molecule peak at m/z 521.2871 $[M + H]^+$ (calcd 521.2903) in the HRFABMS of **2**. Similarly, on the basis of the one-dimensional (Tables 1 and 2) and two-dimensional NMR (Figure 7) spectra, like **1**, compound **2** was also expected to be a meroterpenoid with the same flavanone and bicyclic sesquiterpene components. However, the NOESY correlations of H-1/H-9, H-1/H-7, H-7/H-5, CH_3-8′/H-2′, and H-6/H-15 suggested a different stereochemistry at C-4 (Figure 8). An ECD calculation (Figure

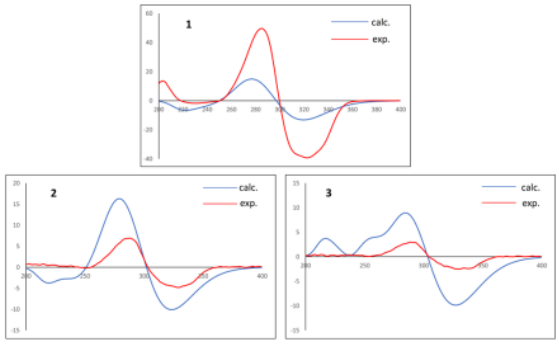

Figure 6. Measured and calculated ECD for **1**−**3**.

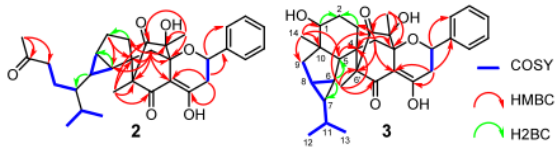

Figure 7. Key COSY, HMBC, and H2BC correlations for **2** and **3**.

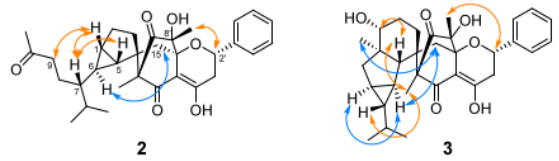

Figure 8. Key NOESY correlations for **2** and **3**.

6) and synchrotron X-ray diffraction analysis indicated the absolute configuration of **2** with a Flack parameter of 0.12(9) (Figure S25). All of the data presented above indicated that compound **2** (syzygioblane B) is the C-4 epimer of **1**.

Compound **3** (syzygioblane C) was isolated as a pale yellow oil and showed a protonated molecule peak at m/z 521.2871 $[M + H]^+$ (calcd 521.2903) corresponding to the molecular formula $C_{32}H_{40}O_6$. The ^{1}H and ^{13}C NMR (Tables 1 and 2) spectra of **3** displayed signal patterns similar to those of **1** and **2** for the flavanone skeleton, the C-2′ to C-5′, C-7′ to C-10′, and C-1″ to C-6″ positions, as well as 4′-OH and 6′,8′-CH_3. The ^{1}H−^{1}H COSY and HMBC correlations (Figure 7) also supported the presence of the same 6,8-dimethylflavanone moiety found in **1** and **2**. Signals for an isopropyl unit, C-11 to C-13, were also observed in the NMR spectra of **3**. The NMR signals for other portions of **3** were dissimilar from those of **1** and **2**, and an additional broad proton was seen at 2.45 ppm, suggesting that compound **3** is also a meroterpenoid containing a 6,8-dimethylflavanone but hybridized with a type of sesquiterpene different from those in **1** and **2**. The ^{1}H−^{1}H COSY for the sesquiterpene side showed correlations of H-8/H-6, H-7, and H-9, of H-7/H-11, and of H-11/H-12 and H-13 (Figure 7). Additional HMBC correlations were found from H-14 to C-1 (shifted downfield at δ_C 77.6), C-5, C-10, and C-9, H-5 to C-4, and H-15 to C-3 and C-4, as well as H2BC correlations between H-1/C-2, H-3/C-2, and H-6/C-5 and C-7. Together, all of the data suggested a tricyclic sesquiterpene with a 6−5−3 ring system, a hydroxy moiety at C-1, an isopropyl unit at C-7, and a methyl group at C-10. The

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Table 3. Antiproliferative Activity Data of Syzygioblanes A−C (1−3, respectively) versus Different Cell Lines[a]

	IC_{50} (μM)[b]					SI[c]
	A549	MDA-MB-231	MCF-7	KB	KB-VIN	KB/KB-VIN
1	7.7	12.0	10.4	5.8	0.4	14.5
2	7.0	13.0	4.4	5.8	0.6	9.7
3	12.1	33.6	26.6	18.1	4.1	4.4
4	>40	>40	>40	>40	>40	–
PXL[d] (nM)	3.2	15.0	13.2	3.0	2372.2	0.001

[a]Abbreviations: A549, lung adenocarcinoma; MDA-MB-231, triple-negative breast cancer (ER-, PR-, and HER2-negative); MCF-7, HER2-negative breast cancer; KB, HeLa derivative, originally isolated from epidermoid; KB-VIN, vincristine resistant KB subline with P-gp overexpressed. [b]Antiproliferative activity expressed as IC_{50} values for each cell line, the concentration of compound that caused 50% reduction relative to untreated cells determined by the SRB assay. [c]SI = non-MDR(IC_{50})/MDR(IC_{50}). [d]Paclitaxel.

relative configurations in **3** were determined from NOESY data (Figure 8), showing correlations of H-15/H-6 and H-14, H-6/H-8, CH_3-6′/H-7 and H-5, H-5/H-1, and CH_3-8′/H-2′. The absolute configurations were determined by ECD calculations (Figure 6).

Meroterpenoids make up an exceptional class of structurally diverse natural products formed by the hybridization of terpenoids and nonterpenoids.[5−8] While few meroterpenoids have been isolated from plants, this compound type is found abundantly in bacteria, fungi, algae, and marine organisms. The most common meroterpenoids are hybrids of terpenoids with polyketides and, to a lesser extent, flavonoids. Although small numbers of meroterpenoids containing flavonoid and cyclic terpenoid components have been reported,[9] in all of them, both components were connected simply. In contrast, complex connections were observed between terpenoids and aromatic polyketides, such as phloroglucinol, syncarpic acid, chromane/chromene, and others.[1]

The newly isolated syzygioblanes A−C (**1**−**3**, respectively) could presumably be biosynthesized through a [4+2] cyclization between the 6,8-dimethylflavanone desmethoxymatteucinol (**4**), which was also isolated from *S. oblanceolatum* in this study, and an appropriate germacrane-based bi- or tricyclic sesquiterpene with an exo-olefin (Figure 9). Fungal meroterpenoids, xenovulenes, were also found to be biosynthesized through an intermolecular hetero [4+2] cyclization between humulene, a sesquiterpene, and tropolones.[10]

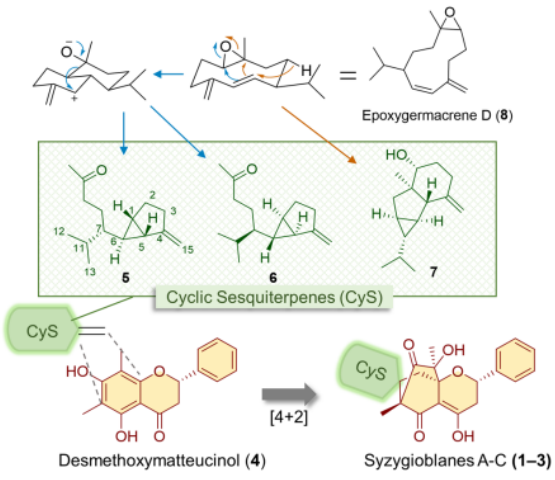

Figure 9. Possible biosynthetic pathway.

Compound **5** and its epimer, **6**, with an exo-olefin on a bicyclo[3.1.0]hexane, which might be biosynthesized through epoxygermacrene-D (**8**),[11] are the necessary sesquiterpene precursors to **1** and **2**, respectively, but they have not yet been isolated from nature. Sesquiterpene **7**, the needed sesquiterpene component for **3**, is a diastereomer of torienol.[12] Compounds **5**−**7** were previously synthesized by the treatment of **8** with basic alumina.[11,13]

Isolated compounds **1**−**3** and **4** for comparison were evaluated for antiproliferative activity against five human tumor cell lines (HTCLs): A549 (lung adenocarcinoma), MDA-MB-231 (triple-negative breast cancer), MCF-7 (HER2-negative breast cancer), KB (HeLa derivative, originally isolated from epidermoid), and KB-VIN (vincristine resistant KB subline with P-gp overexpressed) (Table 3). Compounds **1** and **2** exhibited potent antiproliferative activity against all tested HTCLs with IC_{50} values of 0.42−13.0 μM. Interestingly, compounds **1**−**3** showed greater inhibition of the growth of KB-VIN multidrug resistant cells than of the KB chemosensitive parental subline. In particular, compound **1** showed the most hypersensitivity against KB-VIN with a selective index (SI, the IC_{50} value against KB divided by the IC_{50} value against KB-VIN) of 14.5. This peculiar phenomenon, greater effectiveness against MDR cells than against drug-sensitive cells, is termed collateral sensitivity (CS).[14] In a recent review,[15] ∼70 plant-derived natural products showing CS against drug resistant cancer cells were cited; however, natural products with SI values of >10 and a nanomolar IC_{50} value against MDR cell lines are rare.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c01248.

Experimental procedures, spectroscopic data, ORTEP structure for syzygioblane B (**2**), X-ray structure reports, standard deviation (SD) for antiproliferative activity, and information for the conformers used for ECD calculations (PDF)

Accession Codes

CCDC 2344822 and 2344826 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The

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(3) (a) Syzygioblane A (**1**): colorless amorphous solid; $[\alpha]^{25}_{D}$ −54.8 (*c* 0.10, $CHCl_3$); IR (neat) ν_{max} 2925, 2871, 2360, 2342, 1717, 1710, 1663, 1603, 1457, 1367, 1319, 1283, 1160, 1140, 1070, 990, 933, 917, 850, 751, 700, 669 cm^{-1}; ^1H and ^{13}C NMR data in Tables 2 and 3; HRFABMS *m*/*z* 521.2893 $[M + H]^+$ (calcd for $C_{32}H_{41}O_6$, 521.2903). (b) Syzygioblane B (**2**): colorless amorphous solid; $[\alpha]^{25}_{D}$ −96.2 (*c* 0.10, $CHCl_3$); IR (neat) ν_{max} 3404, 2952, 2871, 2360, 2345, 1725, 1696, 1660, 1602, 1456, 1365, 1322, 1276, 1215, 1185, 1146, 1097, 1049, 989, 934, 924, 850, 816, 760, 701, 669, 599, 529, 464 cm^{-1}; ^1H and ^{13}C NMR data in Tables 2 and 3; HRFABMS *m*/*z* 521.2871 $[M + H]^+$ (calcd for $C_{32}H_{41}O_6$, 521.2903). (c) Syzygioblane C (**3**): pale yellow oil; $[\alpha]^{25}_{D}$ −76.7 (*c* 0.10, $CHCl_3$); IR (neat) ν_{max} 2951, 2872, 2360, 2342, 1730, 1660, 1603, 1453, 1363, 1309, 1217, 1139, 1077, 1034, 856, 749, 699, 669 cm^{-1}; ^1H and ^{13}C NMR data in Tables 2 and 3; HRFABMS *m*/*z* 521.2871 $[M + H]^+$ (calcd for $C_{32}H_{41}O_6$, 521.2903).

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Cyclic Sesquiterpene–Flavanone [4+2] Hybrids, Syzygioblanes A–C, Found in an Indonesian Traditional Medicine, “Jampu Salo” (Syzygium oblanceolatum)

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