Natural Product Synthesis

International Edition: DOI: 10.1002/anie.201700831
German Edition: DOI: 10.1002/ange.201700831

Asymmetric Total Syntheses of *Kopsia* Indole Alkaloids

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Abstract: *The asymmetric total syntheses of a group of structurally complex Kopsia alkaloids, (−)-kopsine, (−)-isokopsine, (+)-methyl chanofruticosinate, (−)-fruticosine, and (−)-kopsanone, has been achieved. The key strategies for the construction of the molecular complexity in the targets included an asymmetric Tsuji–Trost rearrangement to set the first quaternary carbon center at C20, an intramolecular cyclopropanation by diazo decomposition to install the second and third quaternary carbon centers at C2 and C7, respectively, and a SmI_2-promoted acyloin condensation to assemble the isokopsine core. A radical decarboxylation of an isokopsine-type intermediate results in a thermodynamic partial rearrangement to give N-decarbomethoxyisokopsine and N-decarbomethoxykopsine, two key intermediates for the syntheses of Kopsia alkaloids with different subtype core structures.*

Kopsia indole alkaloids[1] (Figure 1, **1**–**12**) are isolated from various *Kopsia* (Apocynaceae) species, which are mainly distributed in Southeast Asia, India, and China. These alkaloids show several impressive types of biological activity, including cholinergic, antirheumatism, and anti-inflammation effects.[2] Although they have a long history in terms of isolation and identification,[3,4] kopsine (**1**) and kopsanone (**12**) were only obtained synthetically in the 1980s, when Magnus et al. reported their total syntheses in racemic forms using an intramolecular Diels–Alder reaction as a key step.[5] The first asymmetric total synthesis of **12** was reported by MacMillan et al. in 2011 using organocatalysis, an intermolecular Diels–Alder reaction, and thermodynamic rearrangement of kopsinic acid as key steps.[6] The asymmetric total synthesis of methyl *N*-decarbomethoxychanofruticosinate (**9**) was recently described by Ma et al. using an anion oxidative coupling as a key step.[7] To the best of our knowledge, however, the total syntheses of fruticosine (**10**) and isokopsine (**5**) have not been reported.

The core skeletons of the kopsine family can be categorized into four subtypes: kopsine, isokopsine, chanofruticosine, and fruticosine. The latter three types are most likely biogenetically derived from the first type by rearrangement and fragmentation (Figure 1). In terms of the synthetic challenge, these alkaloids feature a rigid and cagelike polycyclic skeleton as well as multiple stereogenic centers, including three all-carbon-substituted quaternary carbon centers, the construction of which is considered to be one of the most difficult challenges in synthetic organic chemistry.[8] Herein, we report the asymmetric total syntheses of representatives of all four subfamilies of these alkaloids, namely, kopsine (**1**), isokopsine (**5**), methyl chanofruticosinate (**7**), fruticosine (**10**), and kopsanone (**12**).

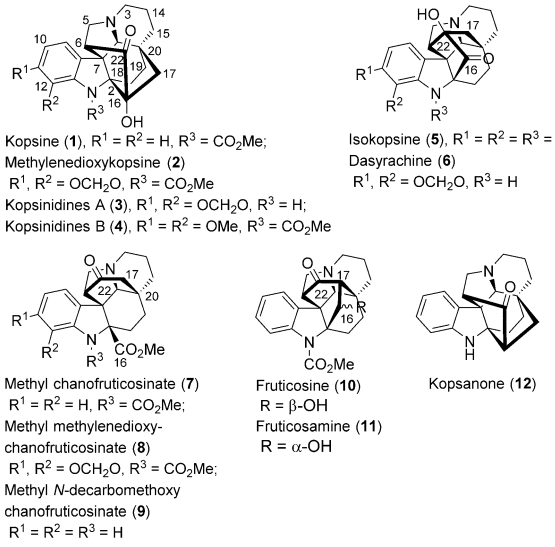

Figure 1. Structures of the representative kopsine-related alkaloids.

Our retrosynthetic analysis is outlined in Figure 2. Based on previous semisynthetic studies it found that switching between the kopsine and isokopsine core skeletons was possible under basic conditions,[4b] and we reasoned that if an isokopsine intermediate such as **13** could be efficiently assembled, then we should be able to generate *N*-decarbomethoxyisokopsine (**15**) by direct radical decarbonylation. *N*-Decarbomethoxykopsine (**16**) then should be readily prepared from **15** by an acyloin rearrangement. Protection of the nitrogen atom in **15** and **16** could afford **5** and **1**, respectively. In turn, **7** and **10** could be obtained by either direct cleavage of the C16–C22 bond in **5** or by reduction of the ketone in **5** first, then cleavage of the C16–C22 bond, followed by an intramolecular aldol addition of the aldehyde **17**. Meanwhile, **12** could be easily generated by dehydroxylation from **16**. We envisioned that a critical nitrile intermediate (**18**) could be generated by forming the C16–C22 bond by a SmI_2 promoted acyloin condensation of **19**.[9] Forming the substituted pyrrolidine ring in **19** from **20** was envisioned by opening of the cyclopropyl ring by a cyano anion at C2, that is, a Strecker-type reaction, followed by a Mannich reaction. We planned to

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Supporting information for this article can be found under: http://dx.doi.org/10.1002/anie.201700831.

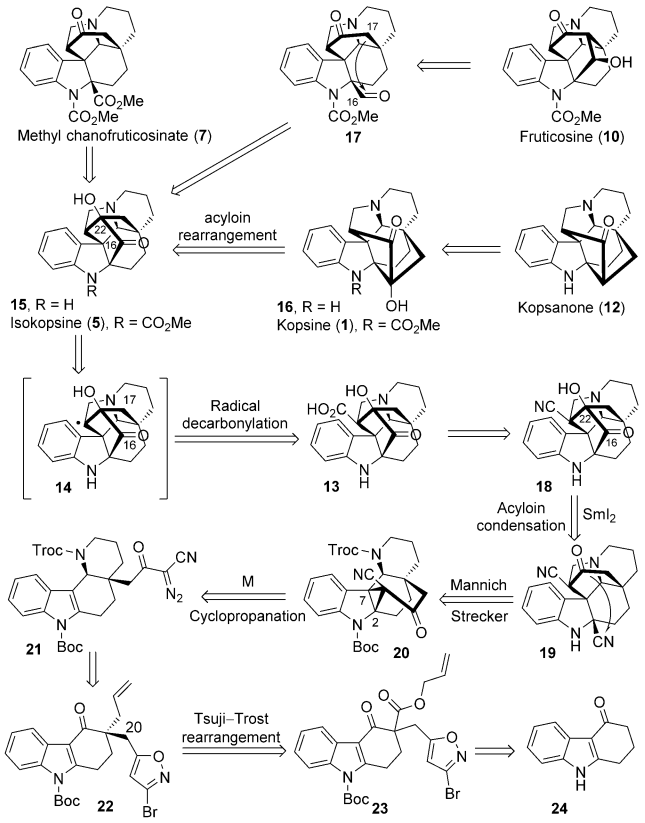
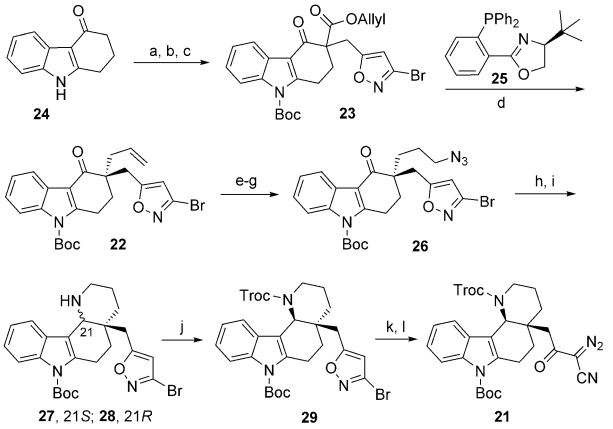


Figure 2. Retrosynthetic analysis of kopsine-related alkaloids. Boc = *tert*-butoxycarbonyl, Troc = 2,2,2-trichloroethoxycarbonyl.



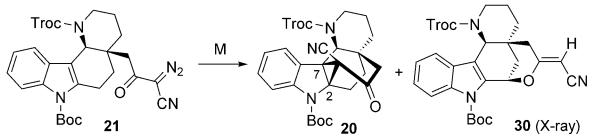
Scheme 1. Preparation of the diazo **21**. Reagents and conditions: a) $(Boc)_2O$, DMAP, DCM, RT, 15 min, 96%; b) LiHMDS, THF, −78 °C, 30 min, then allyl carbonochloridate, −78 °C to RT, 1.5 h, 83%; c) 3-bromo-5-(bromomethyl) isoxazole, K_2CO_3, acetone, reflux, 16 h, 86%; d) $[Pd_2(dba)_3]$ **25**, PhMe, RT, 30 min, then reflux, 3 h, 91%, 94% *ee*; e) benzo[*d*][1,3,2]dioxaborole, $[RhCl(PPh_3)_3]$, THF, RT, 30 min, then $NaBO_3{\cdot}H_2O$, THF/H_2O (v/v 4:1), 85 °C 92%; f) MsCl, TEA, DCM, 0 °C, 15 min; g) NaN_3, DMF, 60 °C, 3 h, 95% over two steps; h) PPh_3, THF/H_2O (V/V 5:1), reflux, 3 h, 91%; i) $NaBH_4$, EtOH/THF (V/V 3:1), RT, 16 h, **27** (85%), **28** (5%); j) TrocCl, Na_2CO_3, DCM/H_2O (V/V 1:1), RT, 1 h, 94%; k) $FeCl_2$, CH_3CN, reflux, 20 min, (l) 1*H*-imidazole-1-sulfonyl azide, pyridine, RT, 3 h, 91% over two steps. dba = dibenzylideneacetone, DCM = dichloromethane, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, DMF = *N*,*N*-dimethylformamide, HMDS = hexamethyldisilazide, Ms = methanesulfonyl, TEA = triethylamine, THF = tetrahydrofuran.

generate the cyclopropyl ring in **20** by a metal-salt-catalyzed diazo decomposition of **21**, a strategy that we used to efficiently construct the quaternary carbon centers at C2 and C7 in previous indole alkaloid syntheses.[10] The diazo **21** could be generated from **22** by opening the isoxazole ring and diazotation. The first quaternary carbon center at C20 could be constructed from **23** by an asymmetric Tsuji–Trost rearrangement.[11,12] The intermediate **23** could be prepared from the commercially available tetrahydrocarbazolone **24**.

As depicted in Scheme 1, we started our synthesis with **24**. Installation of a Boc group on the indole nitrogen atom, followed by two steps, α-acylation and α-alkylation, yielded **23** in 69% yield. Application of an asymmetric Tsuji–Trost rearrangement[11,12] with the oxazole (*S*)-**25** as a catalyst provided **22** in 91% yield and 94% *ee*. This rearrangement was readily implemented on a 50 gram scale without loss of either the yield or the enantioselectivity. Three steps of converting the terminal olefin into an azide group were realized to afford **26** in 87% yield by subsequent borohydration, mesylation, and azide replacement. Transformation of the azide in **26** into an amine with Ph_3P in aqueous THF at 60 °C concomitantly resulted in formation of an imine group at C21, which was then diastereoselectively reduced with $NaBH_4$ in a mixture of EtOH/THF (3:1) to give **27** and **28** in 82% combined yield and a 17:1 ratio over two steps. Protection of the amine in **27** with Troc under basic conditions, followed by two steps of opening of the isoxazole ring with $FeCl_2$ in **29** and diazotation of the resultant β-ketone-α-diazo intermediate furnished **21** in 86% yield.

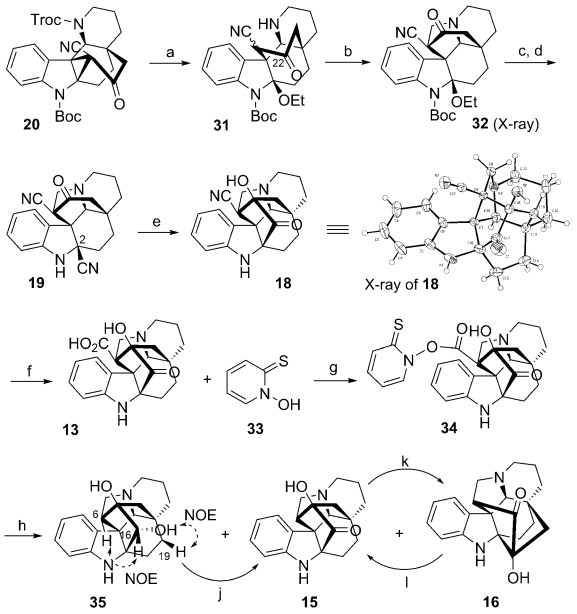
With diazo **21** available, we then evaluated the efficiency of various metal salts as catalysts for the intramolecular cyclopropanation reaction (Table 1). Initial experiments on the diazo decomposition of **21** in CH_2Cl_2 with $[Rh(OAc)_2]$, $Rh(C_3F_7CO_2)_2$, CuOTf, $Cu(OTf)_2$, and $Cu(TBS)_2$ as catalysts gave very disappointing results. In these cases, only the C–H insertion byproduct **30** was obtained in low yields rather than the desired product **20** (entries 1–5). The absolute configuration of **30** was determined by its X-ray crystallographic analysis. To our delight, diazo decomposition of **21** with 20 mol% of either $[Cu(acac)_2]$, $[Cu(tfacac)_2]$, or $[Cu(hfacac)_2]$ in 1,2-dichloroethane (DCE) at 80 °C provided **20** in 10–22% yields and **30** in 12–15% yields (entries 6–8). Using $[Cu(hfacac)_2]$ afforded **20** with the highest yield of 22% (entry 8). To improve the yield of **20**, $[Cu(hfacac)_2]$ was then used as the catalyst in further screening of the solvent and temperature. The yield of **20** was enhanced to 38% when microwave irradiation conditions (120 °C) were applied in DCE (entry 9). Further screening revealed that chlorobenzene was the best solvent for the cyclopropanation reaction when heating at 120 °C for 30 minutes (entries 10–14). Diazo decomposition of **21** on a 5 gram scale with 20 mol% of $[Cu(hfacac)_2]$ provided **20** in an acceptable 52% yield and **30** in 13% yield (entry 12). Successful preparation of **20** by cyclopropanation allowed us to build up two other quaternary carbon centers at C2 and C7, thus propelling us forward toward the target alkaloids.

Table 1: Optimization of cyclopropanation reactions.[a]



Entry	Catalyst	Solvent	T [°C]/t	Yield [%]	
				20	**30**
1	$[Rh(OAc)_2]$	DCM	25/3 h	trace	16
2	$Rh(C_3F_7CO_2)_2$	DCM	25/3 h	none	23
3	CuOTf	DCM	25/3 h	trace	22
4	$Cu(OTf)_2$	DCM	25/3 h	none	18
5	$Cu(TBS)_2$	DCE	80/2 h	none	15
6	$[Cu(acac)_2]$	DCE	80/2 h	10	15
7	$[Cu(tfacac)_2]$	DCE	80/2 h	17	12
8	$[Cu(hfacac)_2]$	DCE	80/2 h	22	13
9[b]	$[Cu(hfacac)_2]$	DCE	120/5 min	38	12
10	$[Cu(hfacac)_2]$	benzene	80/2 h	40	5
11	$[Cu(hfacac)_2]$	chlorobenzene	100/1 h	45	17
12	$[Cu(hfacac)_2]$	chlorobenzene	120/30 min	52	13
13	$[Cu(hfacac)_2]$	chlorobenzene	130/15 min	49	15
14	$[Cu(hfacac)_2]$	1,2-dichloro-benzene	150/10 min	34	13

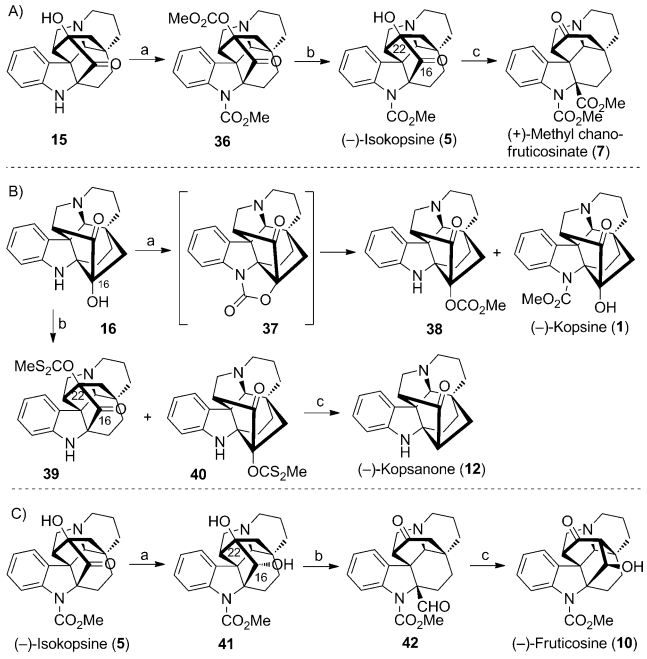
[a] All reactions were performed with 20 mol% catalyst in 0.005 M concentration in freshly dried and argon-sparged solvent.[15] [b] Heating by microwave. acac = acetylacetonyl, hfacac = hexafluoroacetylacetone, TBS = *tert*-butyldimethylsilyl, Tf = trifluoromethanesulfonyl, tfacac = trifluoroacetylacetone.



Scheme 2. Asymmetric approach to the core structure.[15] Reagents and conditions: a) Zn, EtOH/THF/AcOH (v/v/v 15:15:1), RT, 30 min; b) CH_2O (30% aq.), EtOH, reflux, 6 h, 55% over two steps; c) CF_3CO_2H, DCM, 0°C to RT, 1 h, d) TMSCN, $AlCl_3$, DCM, RT, 16 h, 74% over two steps; e) SmI_2 (0.1 M in THF), THF, RT, 15 min, 74%; f) HCl (concentrated), 100°C, 16 h, 81%; g) EDCI, DMAP, DCM, RT, 3 h; h) AIBN, Bu_3SnH, benzene, reflux, 1 h, **35** (11%), **15** (36%), **16** (30%); j) DMP, DCM, RT, 30 min, 36%; k) 1.0 M NaOH aq./1,4-dioxane (v/v 1:1), RT, 5 min, **15** (20.6%), **16** (79.4%); l) 1.0 M NaOH aq./1,4-dioxane (v/v 1:1), RT, 5 min, **16** (84.5%), **15** (15.5%). TMSCN = trimethylsilyl cyanide, EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, DMAP = 4-dimethylaminopyridine, AIBN = azodiisobutyronitrile.

As shown in Scheme 2, the total synthesis was continued using **20** as the starting material. Treatment of **20** with Zn dust in a mixture of EtOH/THF/AcOH resulted in removal of the Troc group and simultaneous opening of the cyclopropane ring to form an iminium cation at C2, which was immediately captured by ethanol to afford the amine **31**. The amine **31** was unstable under chromatography conditions because the secondary amine in **31** was prone to forming an aminal functional group with the carbonyl group at C22. As a result, crude **31** was used directly in the following Mannich step, and afforded the hexacyclic **32** in 55% yield over two steps. Removal of the Boc group in **32** with CF_3CO_2H and subsequent cyanation[13] with TMSCN and $AlCl_3$ provided **19** in 74% overall yield over two steps. All efforts to hydrolyze the cyano group into either an ester group or to protect the indoline nitrogen atom as a methoxycarbonyl group failed at this stage. The cyano group at C2 was very unstable to both acidic and basic conditions. Based on the strategy developed by Wei,[14] SmI_2-mediated acyloin condensation of **19** was employed, and it proceeded smoothly at room temperature in THF to give **18** in 74% yield. The structures of **18** and **32** were unambiguously confirmed by their X-ray crystallographic analyses.[15] After hydrolysis of the cyano group in **18**, the resultant carboxylic acid in **13** was condensed with **33** to give the ester **34**. Without purification, the crude **34** was subjected to radical decarboxylation conditions to afford the diol **35** in 11% yield and **15** in 36% yield, both with an isokopsine skeleton, as well as **16** in 30% yield with a kopsine skeleton. The relative configuration of the hydroxy group at C16 in **35** was confirmed based on the NOE correlations observed between OH-16 and H-19, and H-6 and H-16. Oxidation of **35** with DMP provided **15** in 36% yield. The compound **16** was believed to be an acyloin rearrangement product of **15**, which was confirmed by heating pure **15** in benzene for 1 hour, after which time a mixture of **15** and **16** in a 1:1 ratio was detected. In accordance with literature,[4b] when pure **15** was stirred in a mixture of 1M NaOH and 1,4-dioxane (v/v 1:1) for 5 minutes at room temperature, approximately four-fifths of **15** was converted into **16**. A similar result was observed when pure **16** was stirred in the same reaction mixture, that is, about one-fifth was converted into **15** (Scheme 2).

The late stages of the syntheses of the *Kopsia* family alkaloids are illustrated in Scheme 3. Treating **15** with triphosgene and pyridine followed by heating the reaction mixture with absolute MeOH provided **36**. Without purification, directly heating **36** with pyridine in aqueous MeOH for 16 hours resulted in selective removal of the methoxycarbonate group at C18 to give (−)-isokopsine [(−)-**5**][4b] in 64% yield over two steps (Scheme 3A). Cleavage of the C16–C22 bond in **5** with $Pb(OAc)_4$ afforded (+)-methyl chanofruticosinate [(+)-**7**][4d] in 65% yield. (−)-Kopsine [(−)-**1**][5e] was synthesized from **16** by treating **16** with triphosgene and pyridine in CH_2Cl_2 and then heating the resultant cyclic carbamate **37** in absolute MeOH for 16 hours, and it afforded **38** in 47% yield and (−)-**1**[4j,5e] in 42% yield (Scheme 3B).



Scheme 3. Syntheses of *Kopsia* alkaloids. Reagents and conditions: Scheme 3A: a) BTC, pyridine, DCM, 0°C, 30 min; then MeOH, reflux, 16 h; b) MeOH/pyridine/H_2O (v/v/v 6:1:1), 70°C, 16 h, 64% over two steps; c) $Pb(OAc)_4$, MeOH, RT, 15 min, 65%. Scheme 3B: a) BTC, pyridine, DCM, 0°C, 30 min; then MeOH, reflux, 16 h; **38** (47%), **1** (42%); b) NaH, CS_2; then MeI, THF, −60°C to RT, **39** (35%), **40** (34%); c) AIBN, $(TMS)_3SiH$, PhMe, reflux, 2 h, **12** (77%). Scheme 3C: a) $NaBH_4$, MeOH, RT, 30 min, 86%; b) $Pb(OAc)_4$, MeOH, RT, 15 min; c) MeONa, THF, 0°C, 30 min, 64% over two steps. BTC = bis(trichloromethyl) carbonate, AIBN = azodiisobutyronitrile, $(TMS)_3SiH$ = tris(trimethylsilyl)silane.

Installation of a methyl dithiocarbonate group on the hydroxy group at C16 in **16** under strong basic conditions provided the expected **40** in 34% yield and the byproduct **39** in 35% yield. Heating **40** with AIBN and $(TMS)_3SiH$ in toluene afforded (−)-kopsanone [(−)-**12**][5b,6] in 77% yield. Meanwhile, (−)-fruticosine [(−)-**10**][4j] was prepared from (−)-**5** in 55% overall yield through a three-step procedure of a stereoselective reduction of the ketone in (−)-**5** to give the single diol **41**, cleavage of the C16–C22 bond with $Pb(OAc)_4$ in **41** to yield aldehyde **42**, and finally a stereoselective intramolecular aldol addition to afford (−)-**10** as a single diastereoisomer (Scheme 3C).

In summary, the asymmetric total syntheses of a group of *Kopsia* alkaloids [i.e., (−)-**1**, (−)-**5**, (+)-**7**, (−)-**10**, and (−)-**12**] which belong to four subfamilies has been accomplished within 23 steps. Construction of the molecular complexity in the targets mainly relied on an asymmetric Tsuji–Trost rearrangement, a metal-salt-catalyzed intramolecular cyclopropanation, and a SmI_2-promoted acyloin condensation. A radical decarbonylation resulted in a thermodynamic partial rearrangement of the isokopsine skeleton to the kopsine skeleton, which provided a basis for us to access the different subtype core structures for the synthesis of the individual alkaloids.

Acknowledgments

We are grateful for financial support from the National Natural Science Foundation of China (21572140 and 21132006).

Conflict of interest

The authors declare no conflict of interest.

Keywords: alkaloids · diazo compounds · natural products · rearrangements · total synthesis

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[15] CCDC 1492784 (**18**), 1518567 (**30**), and 1518568 (**32**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

Manuscript received: January 24, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Natural Product Synthesis

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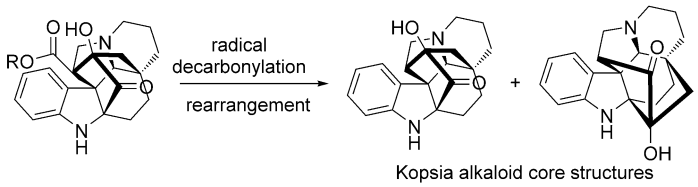
Asymmetric Total Syntheses of *Kopsia* Indole Alkaloids



Kopsia alkaloid core structures

Targeting the core: Asymmetric total syntheses of a group of structurally complex Kopsia alkaloids have been achieved by employing a unified synthetic strategy. Key to the success was an intramolecular cyclopropanation, a SmI_2-promoted acyloin condensation, as well as a radical-based rearrangement process.

