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A Tandem, Nitroalkene Conjugate Addition/[3+2] Cycloaddition Approach to the Synthesis of the Pentacyclic Core of (±)-Scandine

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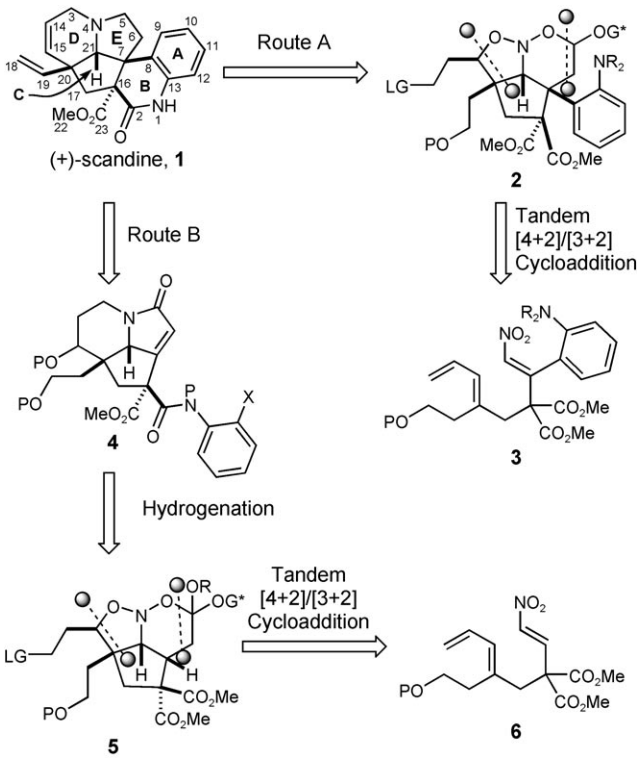
Abstract: The complete pentacyclic core of the melodinus alkaloid scandine has been synthesized. The synthetic strategy features two key steps: (1) a tandem nitroalkene conjugate addition/[3+2] cycloaddition of the resulting silyl nitronate and (2) an intramolecular Heck reaction of an aryl iodide with a γ-disubstituted allylic alcohol which set a highly congested, quaternary stereogenic center with the concomitant formation of an aldehyde. Intramolecular reductive amination with this aldehyde completed the pentacyclic core.

Keywords: conjugate addition; [3+2] cycloaddition; nitroalkenes; quaternary stereogenic centers; silyl nitronates

(+)-Scandine (**1**) is a member of the *Melodinus* alkaloid family,[1] and is biosynthetically related to the *Aspidosperma* class of natural products.[2] Embedded in the pentacyclic core of the molecule resides a central cyclopentyl ring **C** containing all four of the resident stereocenters, three of which are quaternary (Scheme 1).[3] Its densely functionalized structure provided an intriguing challenge to extend the use of the tandem [4+2]/[3+2] nitroalkene cycloaddition process for total synthesis of complex alkaloids.[4,5]

Following a well established analysis for the construction of indolizidines from the tandem cycloaddition of functionalized nitroalkenes,[6] it was envisioned that the core structure of **1** could be assembled by the addition of a chiral vinyl ether to the nitroalkene **3** (Route A, Scheme 1). The application of an intermolecular [4+2]/intramolecular [3+2] approach would not only provide the central cyclopentyl ring, but would also create two of the necessary quaternary centers. However, the requisite nitroalkene for this plan **3**, needed to be both 2,2-disubstituted and bear a geminal diester function next to the reactive center.[7] Not unexpectedly, orienting experiments on a simplified analogue of **3** failed to show the expected [4+2] cycloaddition regardless of the dipolarophile or Lewis acid employed.[8] Thus, an alternative strategy that introduced the C(7) aryl moiety (scandine numbering) at a later stage was envisioned.

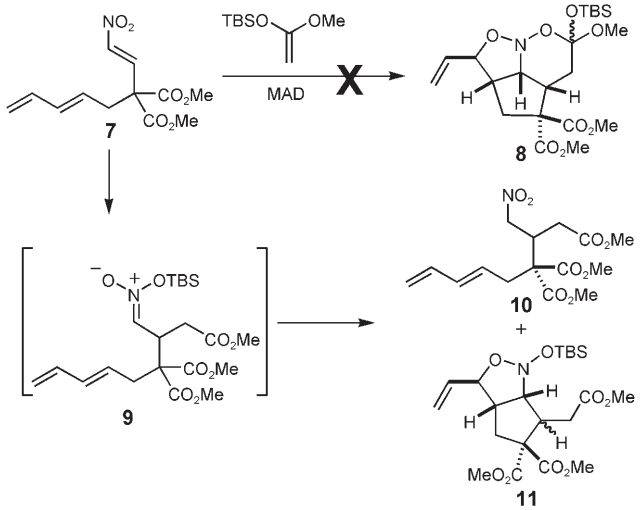
The second generation strategy took good advantage of the tandem [4+2]/[3+2] nitroalkene cycloaddition, but it was still necessary to devise a method to



Scheme 1.

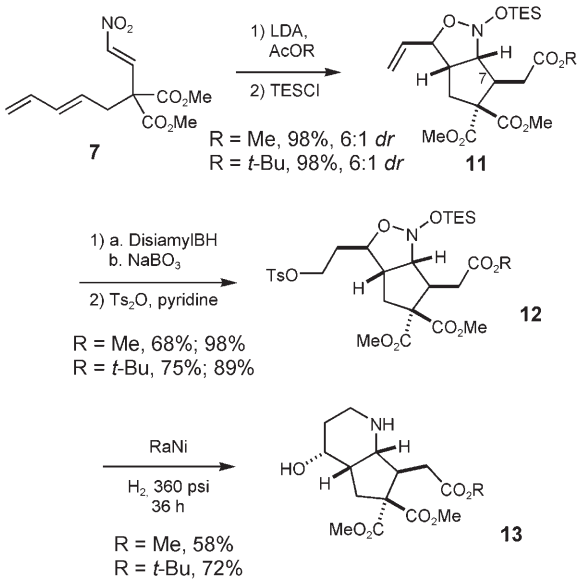
install the C(7) aryl unit and thus create the third quaternary stereogenic center. Both radical-based[9] and Pd-mediated[10] reactions have proven to be reliable methods for the construction of sterically congested quaternary centers. Thus, an unsaturated precursor such as intermediate **4** (Scheme 1) could make use of either of these strategies for the synthesis of (+)-scandine, where intramolecular cyclization would provide the desired lactam (Route B). Interestingly, in no previous study had an indolizidinone been generated directly from the cycloaddition product because that would require the use of a ketene acetal as the dienophile. The construction of the nitroso ortho esters such as **5**, was unexplored within the context of the tandem nitroalkene cycloaddition. Given the need for a highly reactive dienophile to overcome steric encumbrance, the obvious opportunities to investigate the use of chirally modified ketene acetals, and the diversity of transformations available to convert **4** to the scandine core, we were stimulated to reduce this plan to practice.

A simple model study was undertaken first to demonstrate the feasibility of tandem [4+2]/[3+2] nitroalkene cycloaddition with ketene acetals. Nitroalkene **7** was chosen as the test substrate (Scheme 2). If successful, the resulting cycloadducts would also allow investigation into the late-stage intramolecular arylation. Combination of the TBS ketene acetal of methyl acetate with **7** in the presence of MAD as the Lewis acid afforded none of the desired nitroso orthoester **8**. Instead, two non-isomeric compounds were isolated; the first was identified as the conjugate addition product **10**[11] and the second clearly showed the loss of the starting diene and the formation of a monosubstituted alkene. Spectroscopic characterization of this compound revealed that a diastereomeric mixture of the silyl nitroso acetals **11** had formed. This product most likely results from the conjugate addition of the silyl ketene acetal, followed by silyl group migration to provide an intermediate silyl nitronate **9**. Upon warming, this nitronate then undergoes an intramolecular [3+2] cycloaddition with the tethered dipolarophile to provide the silyl nitroso acetal **11**.



Scheme 2.

The construction of nitroso acetal **11** could be streamlined to a one-pot procedure by replacing the silyl ketene acetal of methyl acetate with its lithium enolate, (to effect a Michael-type addition) followed by the *in situ* silylation of the lithium nitronate intermediate with TESCl (Scheme 3). This process also allowed for the incorporation of *tert*-butyl acetates, which were unreactive as the corresponding ketene acetals. With this modified procedure, the silyl nitroso acetal **11** was prepared in high yield, as a 6:1 mixture of two diastereomers. The two diastereomers differed only in the configuration of the C(6) stereocenter [favoring the HC(7)-HC(21) (scandine numbering) *trans* relationship] suggesting that the diastereoselectivity arises from the facial approach of the dipolarophile. Although, this center will be lost in intermediate **4**, it will play a role in the ability to form the lactam precursor (*vide infra*).

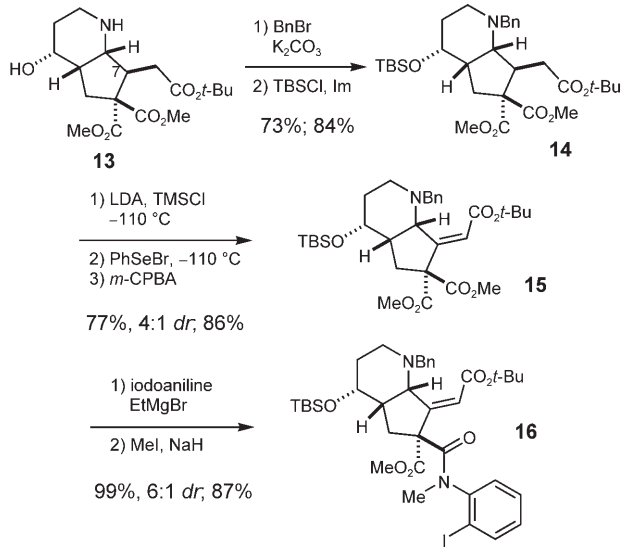


Scheme 3.

The mixture of diastereomeric nitroso acetals was carried forward to the intermediate **12** *via* hydroboration/oxidation of the terminal alkene, followed by tosylation of the resulting primary alcohol. Unexpectedly, in the case of the methyl acetate derived series, hydrogenation of the nitroso acetal under standard conditions with Raney nickel at 360 psi did not provide the desired tricyclic lactam. Instead the bicyclic amino ester **13** was isolated in good yield. Subsequent at-

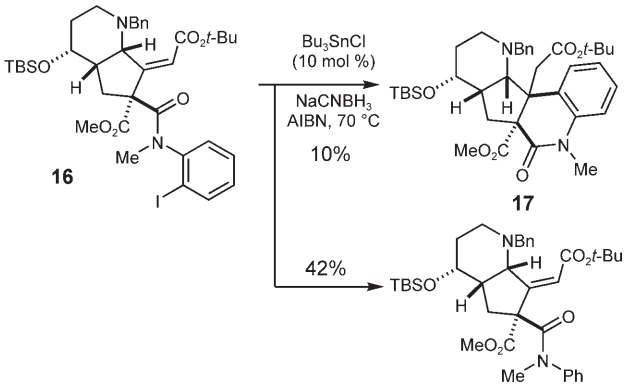
tempts to induce lactamization provided only trace amounts of the cyclization product, suggesting that the C(7) configuration of the major diastereomer of the nitroso acetal was not suited for closure to an all *cis* fused tricyclic lactam. This assumption was proven correct by X-ray crystallographic analysis of the *N*-benzoyl derivative.[12]

Although the stereostructure of **13** did not lend itself to the direct construction of the third ring of the scandine core *via* intermediate **4**, it was still suitable for probing the central question of introducing the C(7) quaternary stereogenic center through intramolecular arylation. The synthetic plan was revised to accommodate the preparation of bicyclic α,β-unsaturated ester **16** (Scheme 4). This approach allows for the correction of the C(7) stereocenter, which will be regenerated during the formation of the quaternary center. Protection of both the alcohol and amine functions provided **14**, which was then dehydrogenated by a two-step selenylation/oxidation procedure to yield **15**, as 4:1 *Z/E* mixtures of geometrical isomers. Interestingly, the selenide had to be prepared using a silyl ketene acetal intermediate at −110 °C to prevent fragmentation of the cyclopentyl ring. Furthermore only the major selenide diastereomer underwent clean oxidation to the corresponding olefin.



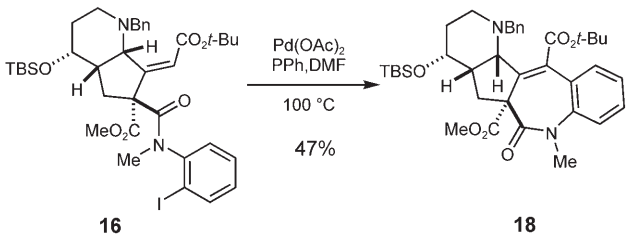
Scheme 4.

The arylation precursor **16** was prepared by selective amidation of the sterically more accessible methoxycarbonyl group of **15**, followed by methylation of the resulting amide. Initial attempts to create the quaternary center were investigated though the generation of an aryl radical (Scheme 5). Unfortunately, only minor amounts of the arylation product **17** were observed. Instead, the reduction of the aryl halide was found to be the major reaction pathway, regardless of the conditions employed. Therefore, the Pd-mediated cyclization was investigated.



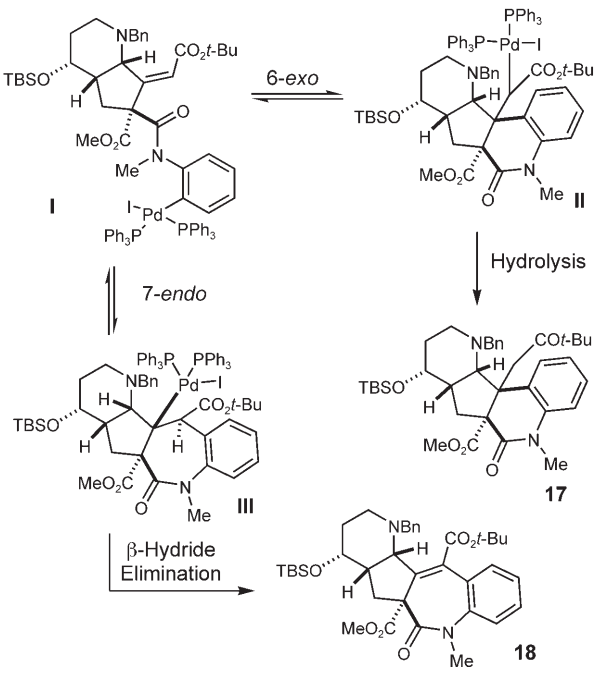
Scheme 5.

The carbopalladative cyclization of **16** cannot proceed by the usual Heck mechanism because of the lack of neighboring hydrogen atoms to allow for β-hydride elimination and catalyst regeneration.[13] In this case the process should lead to a palladium enolate, which could be hydrolyzed upon work-up. However, the addition of a stoichiometric amount of palladium acetate provided only the 7-*endo* cyclization product **18**, and none of the desired 6-*exo* derived lactam **17** (Scheme 6). Despite an expected kinetic preference for the 6-*exo* pathway,[10b] the reversibility of the initial cyclization allows for the formation of the 7-*endo* derived intermediate **III** (Scheme 6). Upon β-hydride elimination to provide **18** (Scheme 7), this pathway is no longer reversible and the reaction is funneled through the 7-*endo* intermediate.[14] The 6-*exo* intermediate **II** can be trapped by the addition of sodium formate,[14] however the desired lactam was isolated in low yield with significant amounts of the deiodinated starting material.



Scheme 6.

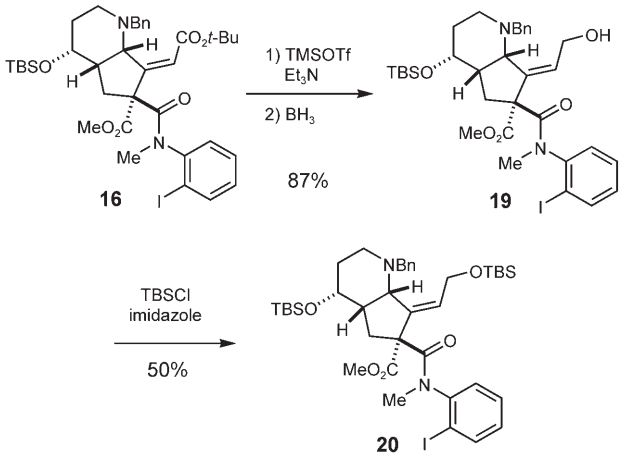
To solve the problem of reversed regioselectivity, we clearly needed to provide a rapid and irreversible capture of the kinetically preferred 6-*exo* cyclization intermediate. This could be accomplished by conversion of the *tert*-butyl ester to a primary alcohol or derivative. Heck type reactions of allylic alcohols and ethers are well precedented and proceed directly to



Scheme 7.

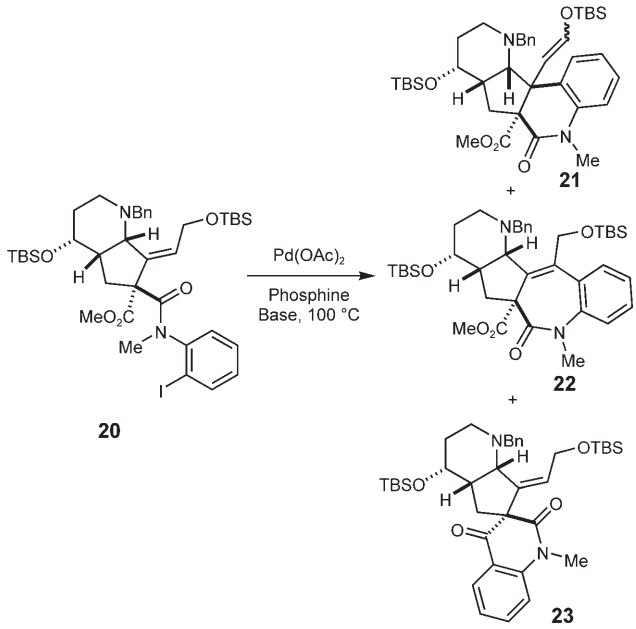
aldehydes or enol ethers by β-hydride elimination.[10a,15] If this pathway is competitive with reversal, the ratio of observed products could be altered. Hydrolysis of the *tert*-butyl ester to the parent acid was required to allow selective reduction to allylic alcohol **19** in the presence of both methyl ester and anilide functions (Scheme 8). The alcohol was then converted to its TBS ether **20** under standard conditions.

The intramolecular arylation of **20** was evaluated under a variety of conditions. As was the case with the corresponding ester, a mixture of both the 6-*exo* (**21**) and 7-*endo* (**22**) derived products was observed along with ketone **23** which arose from arylation of the methyl ester. However, the ratio of the two Heck products could be influenced by changes in solvent, base, ligand, and additive as illustrated in Table 1. The beneficial effect of ammonium salts is well documented in Heck reactions[16] and here, tetrabutylammonium chloride was most effective. The best conditions, entry 6, cleanly provided a 4:1 mixture favoring the desired lactam **21**.



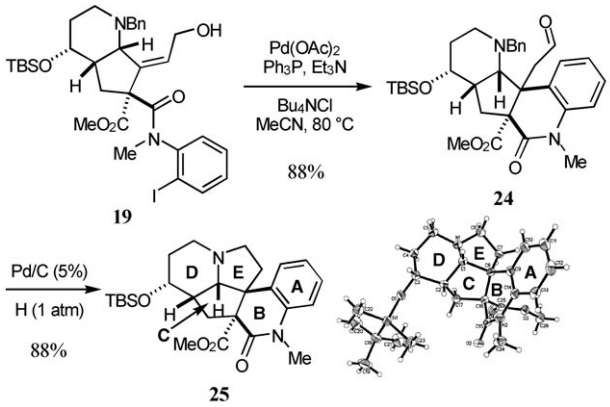
Scheme 8.

Table 1. Optimization of intramolecular arylation of **20**.



Entry	Phosphine	Base	Solvent	Additive	Ratio **21**:**22**:**23**
1	PPh_3	K_2CO_3	DMF	–	0:20:1
2	PPh_3	K_2CO_3	MeCN	–	1:1:1
3	PPh_3	Et_3N	DMF	–	5:1:1
4	PPh_3	Et_3N	MeCN	–	1:0:2
5	–	K_2CO_3	DMF	Bu_4NHClH	1:1:0
6	PPh_3	Et_3N	MeCN	Bu_4NCl	4:1:0
7	P*t*-Bu_3	K_2CO_3	MeCN	Bu_4NCl	1:1:0
8	P*t*-Bu_3	Et_3N	MeCN	Bu_4NCl	3:1:0

Heck reactions of unprotected allylic alcohols are known to provide aldehydes in good yields.[10a,14] Direct use of the primary alcohol would eliminate a protection and deprotection step in the synthesis and the aldehyde would be the ideal intermediate for the subsequent reductive amination step to close the last ring. Thus, exposure of allylic alcohol **19** to the optimized arylation conditions (Table 1) provided the desired 6-*exo* cyclization product **24** in good yield in a 20:1 ratio with the 7-*endo* derived lactam (Scheme 9). Construction of the final ring system could now be readily effected by debenzylation and in situ reductive amination, thus providing the first synthesis of the complete core structure of scandine. X-ray crystal



Scheme 9.

analysis of the amine **25** confirmed the expected connectivity, as well as its relative stereostructure.[12]

In conclusion, we have developed a novel conjugate addition/intramolecular [3+2] cycloaddition sequence that proceeds in high yield and with good diastereoselectivity. This development was necessitated by observed limitations in the tandem [4+2]/[3+2] nitroalkene cycloaddition methodology resulting from the steric bulk of the diene. The preparation of the nitroso acetal **11** allowed for the exploration of an intramolecular aryl cyclization to form a very sterically congested vicinal quaternary center. Currently the completion of the synthesis of (±)-scandine is under study from **25**, as is the development of an enantioselective variant of the conjugate addition/[3+2] cycloaddition step for the total synthesis of (+)-scandine.

Experimental Section

Key Intramolecular Heck Cyclization of 19 to 24.

The reaction was conducted in a 35 mL (one-neck) round-bottom flask, with a gas Intel, septum, stir bar, and reflux condenser, under an atmosphere of argon. To a mixture of $Bu_4NCl{\cdot}H_2O$ (0.493 g, 1.77 mmol, 2.0 equivs.), $Pd(OAc)_2$ (0.020 g, 0.089 mmol, 0.1 equiv.), and triphenylphosphine (0.046 g, 0.177 mmol, 0.2 equivs.) was added a solution of **19** (0.625 g, 0.89 mmol) in acetonitrile (18 mL). To the yellow solution was added triethylamine (0.23 mL, 1.78 mmol, 2.0 equivs.), and the solution was heated to reflux (85 °C, bath temperature) for 12 h. During this time the reaction color became light brown, and a black precipitate began to form. The solution was cooled to room temperature, and was diluted with Et_2O (30 mL). The mixture was washed with H_2O (15 mL), and brine (15 mL). The aqueous layers were combined and back extracted with Et_2O (2×15 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum. The resulting oil was purified by column chromatography (SiO_2, hexanes/acetone/triethylamine, 10/1/0.1 → 8/2/0.1) to give a slightly yellow oil. The oil was dissolved in Et_2O (15 mL) and was washed with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL), H_2O (10 mL), and brine (10 mL). The aqueous layers were back extracted with Et_2O (2×10 mL). The organic layers were combined, dried over $MgSO_4$, and concentrated under vacuum to provide **20** (yield: 0.451, 88 %) as a colorless oil. An analytical sample was obtained by recrystallization (hexanes/EtOAc, −20 °C), providing **24** as colorless prisms.

Analytical Data for 24: mp 145–147 °C (hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.39 [s, 1H, HC(2^{v})], 7.00–7.30 [m, 9H, HC(1–4) HC(3‴–5‴)], 4.01 [s, 1H, HC(8)], 3.49 [s, 3H, HC(2′)], 3.45 [m, 2H, HC(1‴), HC(1^{v})], 3.44 [s, 3H, HC(12)], 3.09 [m, 4H, HC(11a), HC(10), HC(1‴), HC-(1^{v})], 2.85 [ABX, 2H, HC(7)], 2.46 [dt, J = 3.2, 13.9 Hz, 1H, HC(10)], 2.27 [dt, J = 5.6, 9.3 Hz, 1H, HC(7a)], 1.48 [tt, J = 2.9, 11.2 Hz, 1H, HC(9)], 1.38 [m, 1H, HC(9)], 0.97 [s, 9H, HC(2″)], 0.16 [s, 3H, HC(3″)], 0.08 [s, 3H, HC(3″)]; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 201.68 [C(2^{v}], 171,17 [C(1′)], 168.22 [C(6)], 139.41 [C(11c)], 138.19 [C(2‴)], 128.84 [C(3‴)], 128.34 [C(4‴)], 128.23 [C(1)], 128.02 [C-(5‴)], 127.17 [C(3)], 126.58 [C(4a)], 123.10 [C(2)], 115.19 [C(4)], 68.89 [C(11a)], 65.21 [C(8)], 63.14 [C(1‴)], 59.09 [C(6a)], 53.35 [C(2′)], 52.92 [C(1^{v})], 41.85 [C(12)], 41.40 [C(10)], 34.88 [C(7a)], 31.51 [C(7)], 30.74 [C(11b)], 27.07 [C(9)], 26.07 [C(2″)], 18.38 [C(1″)], −4.52 [C(3″)], −4.78 [C-(3″)]; IR ($CDCl_3$): ν = 2952 (m), 2926 (m), 2854 (w), 1731 (s), 1716 (s), 1659 (s), 1600 (m), 1471 (m), 1458 (s), 1373 (s), 1249 (s), 1051 cm^{-1} (m); MS (ESI): m/z = 577 (M^+, 100); TLC: R_f = 0.21 (CH_2Cl_2/MeOH, 18/1, UV); anal. calcd. for $C_{33}H_{44}N_2O_5Si$ (576.80): C 68.72 %, H 7.69 %, N 4.86 %; found: C 68.67 %, H 7.86 %, N 4.96 %.

Acknowledgements

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