Enantioselective Total Synthesis of Wieland–Gumlich Aldehyde and (−)-Strychnine

Daniel Solé, Josep Bonjoch,* Silvina García-Rubio, Emma Peidró, and Joan Bosch*[a]

Abstract: A total synthesis of (−)-strychnine in 15 steps from 1,3-cyclohexanedione in 0.15% overall yield is described. The sequence followed in the assembling of rings is: E → AE [2-(2-nitrophenyl)-1,3-cyclohexanedione] → ACE (3a-aryloctahydroindol-4-one) → ACDE (arylazatricyclic core) → ABCDE (strychnan skeleton) → ABC-DEF (Wieland–Gumlich aldehyde) → ABCDEFG (strychnine). The key steps of the synthesis are the enantioselective construction of the 3a-(2-nitrophenyl)-octahydroindol-4-one ring system and the closure of the piperidine ring by a reductive Heck cyclization to generate the pivotal intermediate (−)-**14**. In contrast, a Lewis acid promoted α-alkoxypropargylic silane-enone cyclization did not lead to synthetically useful azatricyclic ACDE intermediates. The introduction of C-17 and the closure of the indoline ring by reductive amination of the α-(2-nitrophenyl) ketone moiety complete the strychnan skeleton from which, via the Wieland–Gumlich aldehyde, the synthesis of (−)-strychnine is achieved.

Keywords: alkaloids · natural products · nitrogen heterocycles · palladium · total synthesis

Introduction

The classical total synthesis of strychnine by Woodward[1] in 1954 represented a milestone in the field of organic synthesis. Considering its molecular weight, strychnine is one of the most complex natural products: only twenty-four skeletal atoms are assembled in seven rings, resulting in six stereogenic centers five of them in the core cyclohexane ring. Probably because of its complexity, and also its pharmacological and extremely toxic properties,[2] strychnine has always fascinated synthetic organic chemists,[3] although it was not revisited until almost forty years after the first synthesis.[4] Five research groups have succeeded in synthesizing this mythical molecule in recent years, either via isostrychnine[5] or via the Wieland–Gumlich aldehyde[6] (Scheme 1).[7] Two of those syntheses[6c,d] have culminated in the enantioselective total synthesis of the natural enantiomer (−)-strychnine.[8]

In fact, strychnine is probably the most representative of the *Strychnos* alkaloids,[9] a broad group of indole alkaloids, most of them with a common pentacyclic ABCDE skeleton, a two-carbon chain at C-20, and an oxidized one-carbon substituent at C-16.[10] Taking advantage of these common structural features during the last decade we have developed a general and flexible synthetic entry to the *Strychnos* alkaloids,[11] involving the elaboration of the indole nucleus in the last synthetic steps. Our synthesis utilizes a common hexahydroindolone intermediate **2** (see Scheme 2), which incorporates a latent indole ring (the nitrophenyl ketone moiety) and has the required functionality (an enone) for the closure of the piperidine D ring. The versatility of this strategy lies in the fact that, depending on the functionality present in the substituent on the nitrogen, closure of the piperidine ring (bond formed C-15/C-20) can be effected by different methodologies to give azapolycyclic compounds bearing different piperidine substituents, which can be further elaborated into the variety of two-carbon substituents present at C-20 in *Strychnos* alkaloids. In fact, we have employed three different procedures for the closure of the bridged piperidine D ring: i) an intramolecular Michael-type conjugate addition;[11a,e] ii) a $Ni(COD)_2$-promoted biscyclization,[11b,c,e] and iii) an intramolecular cyclization of an enone-propargylic silane system[11d,e] (Scheme 2). As the key hexahydroindolone **2** is also accessible in nonracemic form as a result of the prochiral character of its precursor, a 2-allyl-2-aryl-1,3-cyclohexanedione, our approach also makes possible the enantioselective synthesis of *Strychnos* alkaloids.[11e, 12]

The application of the above strategy to the enantioselective synthesis of strychnine requires the construction of a pentacyclic ABCDE system bearing substituents at C-16 and C-20 with the appropriate functionality for the building of the two additional rings at the final stages of the synthesis. We detail here our studies in this context, which have culminated in a new, short synthesis of (−)-strychnine from the 3a*R*,7a*S* enantiomer of the key intermediate **2**.[8]

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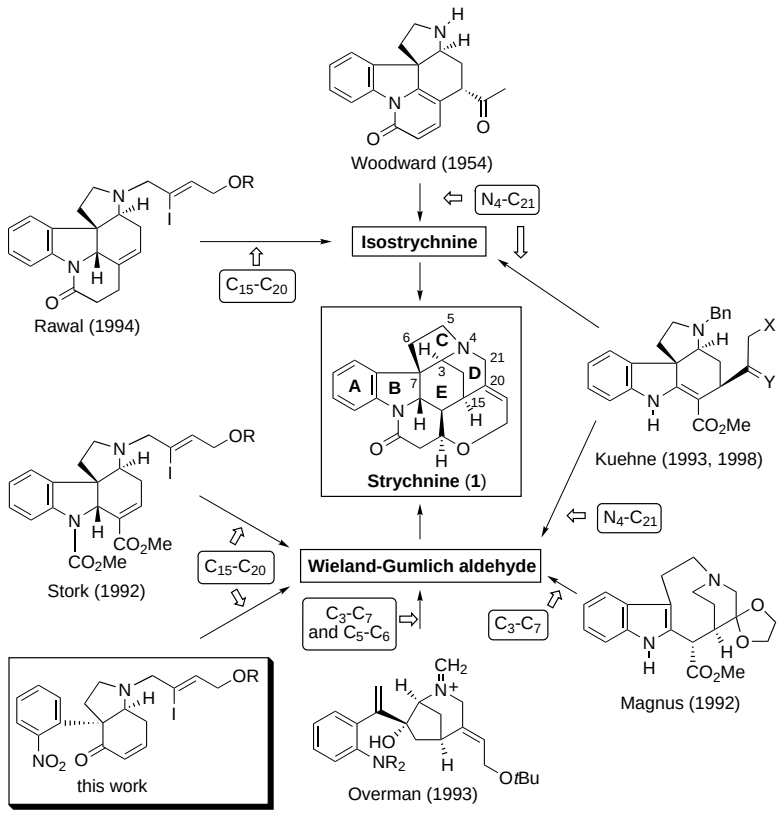

Scheme 1. Previous syntheses of strychnine.

Results and Discussion

Initial plans and results: the propargylic silane approach

Bearing in mind the known easy conversion of Wieland–Gumlich aldehyde to strychnine,[13] we focused our attention on the synthesis of this aldehyde. Consequently, we needed to install a hydroxyethylidene substituent with an *E* stereochemistry at the piperidine 3-position (C-20) during the closure of the piperidine ring and introduce a formyl substituent at C-16. Two of the methodologies we had explored for the closure of the piperidine D ring of *Strychnos* alkaloids seemed to be promising a priori for the stereoselective elaboration of C-20 *E*-configurated double bond: the intramolecular conjugate addition of a propargylic silane upon an enone and the metal-promoted cyclization of a vinyl iodide upon an alkene. Initially, we planned to take advantage of the former methodology. Thus, the use of a propargylic silane **3** bearing an α-alkoxy substituent would generate an alkoxyvinylidene side chain (i.e., **A**)[14] that could be further elaborated into the required 20(*E*)-hydroxyethylidene substituent (Scheme 3).

To develop this approach we focused our attention on the bicyclic propargylic silanes **3a** and **3b** (see Scheme 5), which should be easily accessible by alkylation of **2** with propargylic halides **7a** and **7b**, respectively. These alkylating agents were prepared as outlined in Scheme 4. Reaction of 4-[(*tert*-butyldimethylsilyl)oxy]-2-butynal (**4**)[15] with tris(trimethylsilyl)aluminum etherate resulted in an efficient transfer of a nucleophilic trimethylsilyl group[16] by 1,2-addition to the aldehyde; this affords an α-silyl aluminum alkoxide[17] which was trapped in situ with either acetic anhydride or (methoxymethyl)chloride (MOMCl) to provide α-alkoxypropargylic silanes **5a**,**b**. Selective removal of the TBDMS protecting group by treatment with 10-camphorsulfonic acid (CSA),[18] followed by reaction of the resulting propargylic alcohols **6a**,**b** with methyltriphenoxyphosphonium iodide gave the corresponding iodides **7a**,**b**.

Alkylation of racemic hexahydroindolone **2**[11e, 19] with propargylic iodides **7a,b** afforded the required enone-propargylic silane derivatives **3a,b**. However, contrary to our interests, although the expected closure of the piperidine ring did occur on treatment of **3a,b** with Lewis acids, the desired 20-vinylidene derivatives **A** were not obtained; three different products, alcohol **8**, ketone **9**, and cyclopropane **10**,[20] were isolated from the reaction mixtures instead. The outcome of the cyclization was slightly different depending on the Lewis acid employed (Scheme 5, Table 1). Starting from **3a**, the best overall yields were obtained using $BF_3 \cdot Et_2O$: Alcohol **8** was formed as the major product along with variable amounts of ketone **9**. Increasing reaction temperatures resulted in the formation of considerable amounts of cyclopropane **10**. The

Abstract in Spanish: *Se describe la síntesis total de la (−)-estricnina a partir de la 1,3-ciclohexanodiona mediante un proceso de 15 etapas sintéticas con un rendimiento global del 0.15 %. La estrategia sintética utilizada implica la siguiente secuencia de ensamblaje de anillos: E → AE [2-(2-nitrofenil)-1,3-ciclohexanodiona] → ACE (3a-ariloctahidroindol-4-ona) → ACDE (núcleo arilazatricíclico) → ABCDE (esqueleto de estricnano) → ABCDEF (aldehído de Wieland–Gumlich) → ABCDEFG (estricnina). Las etapas clave de la síntesis son la construcción enantioselectiva del sistema de 3a-(2-nitrofenil)-octahidroindol-4-ona y el cierre del anillo de piperidina para generar el intermedio azatricíclico clave (−)-**14**, que se realiza mediante una ciclación de Heck reductiva. En cambio, una ciclación intramolecular α-alcoxipropargilsilano-enona promovida por ácidos de Lewis no condujo a intermedios azatricíclicos ACDE de interés sintético. La introducción del carbono C-17 y el cierre del anillo de indolina mediante aminación reductiva de la agrupación de α-(2-nitrofenil) cetona completan el esqueleto de estricnano, a partir del cual, a través del aldehído de Wieland–Gumlich, se accede a la (−)-estricnina.*

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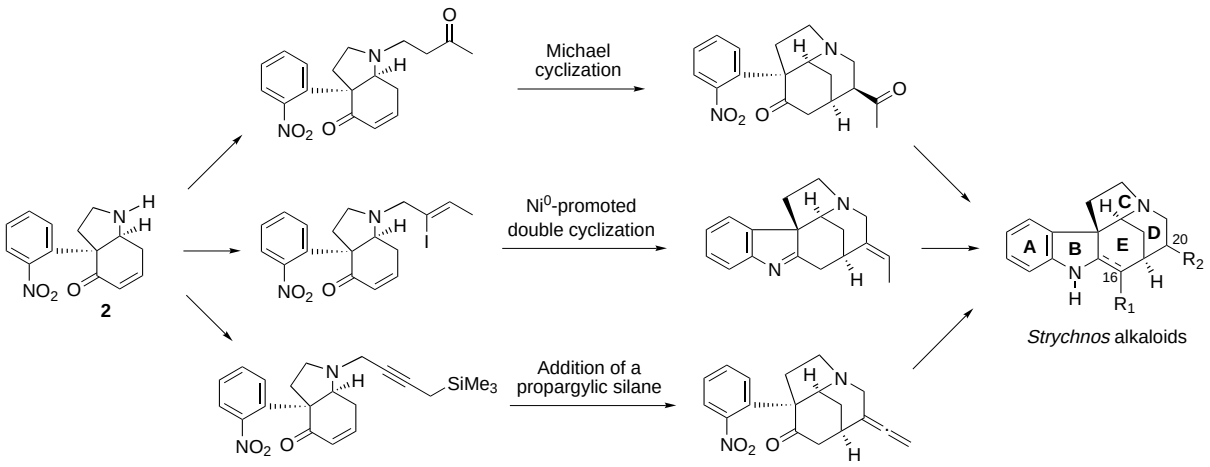
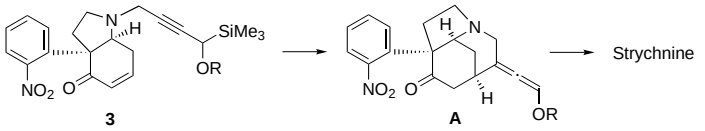
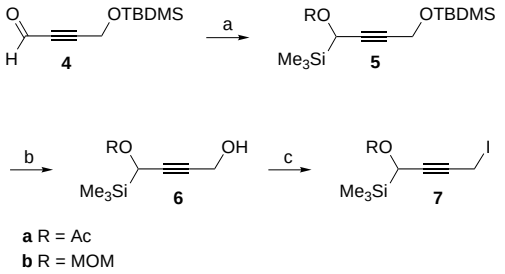


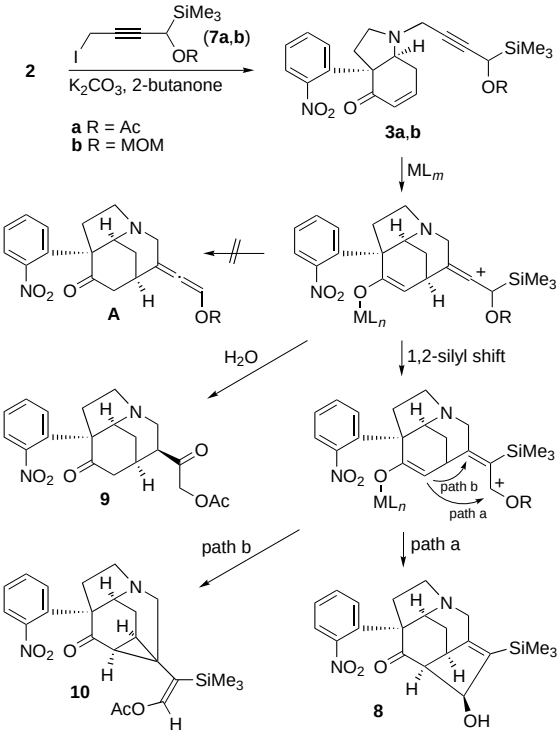
Scheme 2. Synthesis of *Strychnos* alkaloids.



Scheme 3. First synthetic approach to strychnine.



Scheme 4. Synthesis of propargylic iodides **7a** and **7b**. a) $(Me_3Si)_3Al \cdot Et_2O$, Et_2O/pentane, −78 °C, then Ac_2O, 4-DMAP, 25 °C, 57 %, or MOMCl, DIPEA, 25 °C, 30 %; b) CSA, CH_2Cl_2/MeOH, 25 °C, 53 % (**6a**), 63 % (**6b**); c) $(PhO)_3P^+MeI^-$, DMF, 0 °C, 82 %.



Scheme 5. Lewis acid-promoted cyclization of propargylic silanes **3a** and **3b**.

use of $TiCl_4$ gave alcohol **8** as the only product, although in lower yields (26–33 %), whereas $EtAlCl_2$ led to complex mixtures from which cyclopropane **10** was isolated as the major product. On the other hand, treatment of propargylic silane **3b** with $BF_3 \cdot Et_2O$ afforded alcohol **8** (55 %) as the only identifiable product.

The unexpected course of the Lewis acid-promoted cyclization of propargylic silanes **3a**,**b** can be rationalized as outlined in Scheme 5. Instead of the expected desilylation leading to allene **A**, the vinylic carbocation generated in the conjugate addition of the propargylic silane to the enone moiety undergoes a rapid 1,2-silyl shift to give a more stable allylic α-oxycarbocation, which can follow two competing reaction pathways. Intramolecular nucleophilic attack of the

Table 1. Lewis acid-promoted cyclizations of propargylic silanes **3a**,**b**.

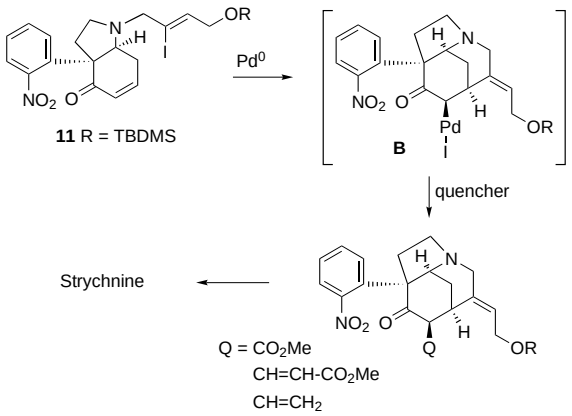
Entry	Propargylic silane	Lewis acid	Solvent	T [°C]	t [h]	**8** [%]	**9** [%]	**10** [%]
1	**3a**	$BF_3 \cdot Et_2O$[a]	CH_2Cl_2	25	20	53–57	8–16[c]	–
2	**3a**	$BF_3 \cdot Et_2O$[a]	CH_2Cl_2	reflux	5	42	10[c]	20
3	**3a**	$TiCl_4$[b]	CH_2Cl_2	25	3	33	–	–
4	**3a**	$TiCl_4$[b]	toluene	80	2	26	–	–
5	**3a**	$EtAlCl_2$[a, d]	toluene	60	1	–	< 5	10–20
6	**3b**	$BF_3 \cdot Et_2O$[a]	CH_2Cl_2	25	20	55	–	–

[a] 4 equiv. [b] 6 equiv. [c] Trace amounts of the C_{20} epimer. [d] Complex reaction mixture.

enolate on the less substituted end of the allylic cation (path a), with subsequent hydrolysis of the ester or ether function during the work up yields cyclopentanol **8**.[21] Alternatively, nucleophilic attack of the enolate on the more substituted end of the allylic cation (path b) leads directly to cyclopropane **10**. Diketone **9** presumably arises from the presence of adventitious water during the reaction.

The intramolecular Heck-type reaction: completion of the CDE core

In light of the above results we turned our attention to a more direct strategy for the introduction of the hydroxyethylidene substituent, consisting in the Pd-catalyzed cyclization of a vinylic iodide upon the enone moiety (Scheme 6). Intramolecular coupling reactions of vinyl halides with alkenes



Scheme 6. Second synthetic approach to strychnine.

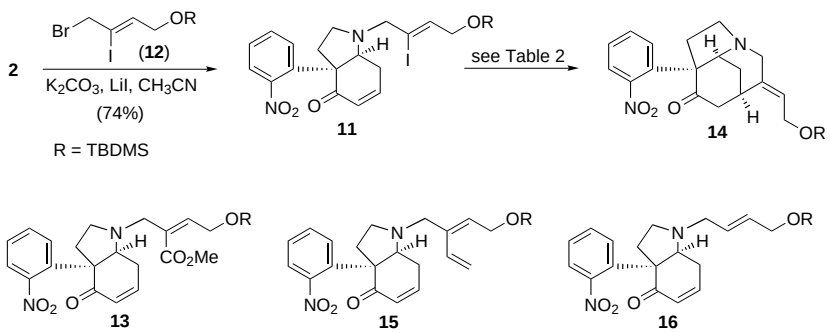
have proved to be useful for the closure of the piperidine ring of *Strychnos* alkaloids (bond formed C-15/C-20), in a process resulting in the stereoselective incorporation of an exocyclic *E*-ethylidene[22] or *E*-hydroxyethylidene[23] double bond at C-20. Our intention was to take advantage of a tandem Pd-promoted cyclization-capture process that would allow both the closure of the hydroxyethylidene-bearing piperidine ring and the introduction of an appropriate substituent at C-16. Thus, we expected that the transient alkylpalladium intermediate **B** arising from the cyclization, with no β-hydrogen available for β-elimination, would be stable enough to be intermolecularly trapped with a suitable quencher.[24]

The required 3a-arylhexahydroindol-4-one (**11**) was prepared by alkylation of racemic **2**[19] with allylic bromide **12**.[25] Disappointingly, all attempts to promote a tandem cyclization-capture process from **11** under a variety of experimental conditions failed (Scheme 7 and Table 2). Thus, treatment of **11** with several Pd catalysts at 1–3 atm of CO[24a] in the presence of MeOH (entries 1–3, Table 2) did not afford cyclized products bearing the C-16 methoxycarbonyl group; only ester **13** resulting from methoxycarbonylation of the initially formed vinyl palladium intermediate was isolated, although in low yield. Unfortunately, under the above conditions, cyclization was not fast enough to compete with direct carbonylation. On the other hand, when the reaction was carried out in the presence of LiCN[24b] as the trapping agent (entry 4, Table 2), the azatricyclic compound **14**, which lacks the C-16 substituent, was the only isolable compound. Using methyl acrylate[24c] in order to introduce a three-carbon substituent at C-16 gave complex reaction mixtures, from which the *N*-unsubstituted amine **2** was isolated together with small amounts of **14** (entry 5, Table 2).

Although the Pd-promoted tandem cyclization-cross coupling processes involving the interception of σ-alkylpalladium intermediates with vinylic stannanes have been described,[24d] treatment of **11** with the Pd catalyst in the presence of tributylvinyltin did not afford the desired product; only azatricyclic compound **14** and diene **15**, formed by a premature intermolecular cross-coupling reaction, could be isolated from the reaction mixtures (entries 6–8, Table 2).

Besides the relatively small difference between cyclization and direct coupling rates, the main problem seemed to be the failure of the trapping agent to intercept the σ-alkylpalladium intermediate **B**. It should be noted that a critical difference between the previously reported successful tandem cyclization-capture processes[24] and the process depicted in Scheme 6 is that the intermediate **B** is not a simple σ-alkylpalladium complex but is actually the keto tautomer of a palladium enolate.[26] In this context, it is known that in the Heck reaction with electron deficient olefins two competing reaction pathways can operate,[27] namely substitution (involving β-H elimination) and 1,4-conjugate addition (involving reduction of the σ-alkylpalladium intermediate), the latter being a variant of the Heck reaction that has received comparatively little attention from the synthetic standpoint.[28] In fact, azatricyclic compound **14** can be envisaged as the 1,4-conjugate addition product. For this reason, we decided to take advantage of this Pd-promoted reductive cyclization and introduce the functionalized C-17 carbon atom later in a subsequent synthetic step.

Although there is some controversy[29] about the nature of the reducing agent in the reductive form of the Heck reaction, tertiary amines with α-hydrogen atoms such as Et_3N are assumed to be the reductants in most cases.[30] After consid-



Scheme 7. Pd-promoted cyclization of vinyl iodide **11**.

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Table 2. Pd-promoted cyclizations of vinylic iodide **11**.

Entry	Catalyst (equiv)	Additives (equiv)	Solvent (ratio)	T [°C] (t [h])	Products[%]
1	$Pd(PPh_3)_4$ (1)	CO[a]	C_6H_6/CH_3CN	100 (4.5)	**13** (36)
		MeOH (8), TEA (2)	1:1		
2	$Pd(OAc)_2$ (0.5)	CO[b]	C_6H_6	80 (1)	**13** (30)
	PPh_3 (1)	MeOH (8), Et_4NCl (2)			
3	$Cl_2Pd(PPh_3)_2$ (0.5)	CO[b], TEA (4)	MeOH/DMF	90 (5)	**13** (20)
			1:2		
4	$Pd(OAc)_2$ (0.5)	LiCN (3.6)	C_6H_6	80 (24)	**14** (5)
	PPh_3 (1)				
5	$Pd(PPh_3)_4$ (0.5)	CH_2=$CHCO_2Me$ (5)	CH_3CN	82 (1)	**2** (45)
		TEA (2)			**14** (5)
6	$Pd(OAc)_2$ (0.5)	Bu_3SnCH=CH_2 (1.2)	C_6H_6	80 (4)	**14** (15)
	PPh_3 (1)	Ag_2CO_3 (2)			**15** (42)
7	$Pd(PPh_3)_4$ (0.5)	Bu_3SnCH=CH_2 (1.1)	THF	66 (2)	**14** (35)
		CuI (1)			**15** (47)
8	$Pd(OAc)_2$ (0.5)	Bu_3SnCH=CH_2 (1.1)	DMF	90 (2)	**2** (20)
		TBACl (1.2)			**14** (5)
		DIPEA (2.5)			**15** (15)
9	$Pd(OAc)_2$ (0.5)	none	TEA	90 (0.5)	**14** (56)
	PPh_3 (1)				
10	$Pd(OAc)_2$ (0.3)	none	TEA	90 (1)	**14** (53)
	PPh_3 (0.6)				
11	$Pd(OAc)_2$ (0.4)	none	DIPEA	95 (5)	**14** (46)
	PPh_3 (0.8)				
12	$Pd(OAc)_2$ (1)	TEA (2)	THF[c]	66 (1.5)	**14** (43)
	PPh_3 (2)				
13	$Pd(OAc)_2$ (0.5)	TEA (2)	THF	66 (27)	**14** (42)
	PPh_3 (1)				
14	$(CH_3CN)_2PdCl_2$ (0.5)	Bu_3SnH (1.1)	C_6H_6	80 (1)	**14** (15)
	PPh_3 (1)				**16** (43)
15	$Pd(OAc)_2$ (0.5)	Et_3SiH (1.1)	THF	66 (1)	**14** (13)
	PPh_3 (1)				**16** (30)

[a] 3 atm. [b] 1 atm. [c] The use of other solvents resulted in lower yields of **14**: DMF, 10%; CH_3CN, 29%.

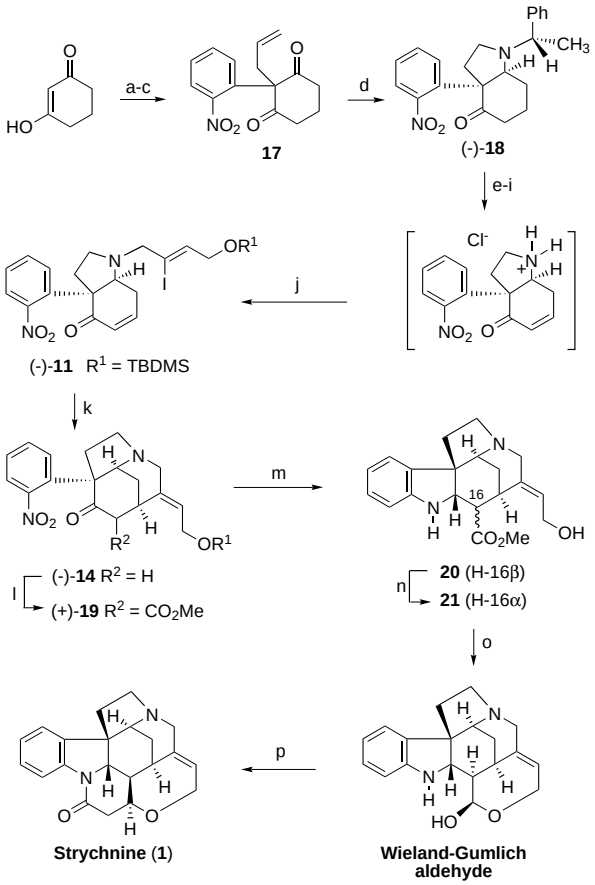
erable experimentation, optimum conditions for the cyclization of **11** were found with the use of $Pd(AcO)_2$ and PPh_3 as the catalyst in Et_3N at 90 °C (entries 9 and 10, Table 2). Under these conditions the intramolecular Pd-catalyzed (0.3 equiv) conjugate addition of **11** (entry 10, Table 2) afforded the azatricyclic derivative **14** in acceptable yield (53%). Bases and solvents other than Et_3N were also examined. DIPEA was less efficient from the synthetic standpoint and gave the best result (46%) when operating with 0.4 equiv of $Pd(AcO)_2$ (entry 11, Table 2). Although the cyclized product **14** could also be obtained in acceptable yield in THF containing Et_3N (entries 12 and 13, Table 2), other solvents such as DMF or CH_3CN gave very low yields. The use of K_2CO_3, Ag_2CO_3, and NaOAc as the base in different solvents resulted in worse yields. Finally, the use of Bu_3SnH[31] (entry 14, Table 2) or Et_3SiH[32] (entry 15, Table 2) as reductants[33] resulted in the formation of the uncyclized reduced product **16** and the desired azatricyclic compound **14**; this gives evidence once again that cyclization was not fast enough to compete with the premature capture of the vinylpalladium intermediate.

The retention of the stereochemistry at the C-20 double bond after the Pd-catalyzed ring closure was inferred from the ^{13}C NMR chemical shifts of C-15 (δ 31.0) and C-21 (δ 54.3) in **14**. These values are in agreement with an *E* configuration for the *O*-protected hydroxyethylidene chain as they are indicative of the steric interaction between C_{15}-H (but not C_{21}-H) and the bulky *tert*-butyldimethylsilyloxymethyl group.

The total synthesis of (−)-strychnine

Once a convenient procedure for the incorporation of the *E*-hydroxyethylidene chain at the piperidine 3-position in the racemic series was established, synthesizing enantiopure **14**, with the natural configuration at the stereogenic centers was simply a matter of starting from the appropriate enantiopure vinyl halide **11**. This compound was obtained in enantioenriched form as outlined in Scheme 8, taking advantage of the short procedure we had developed for the preparation of *cis*-3a-(2-nitrophenyl)octahydroindol-4-ones, consisting in the ozonolysis of 2-allyl-2-aryl-1,3-cyclohexanedione (**17**), followed by a double reductive amination from the resulting diketo aldehyde.[34] The use of α-(*S*)-methylbenzylamine as the aminocyclization agent resulted in the generation of the chiral nonracemic octahydroindolone (−)-**18** (97:3 mixture of *cis* diastereomers) in 37% yield.[11e] N-Dealkylation of (−)-**18** via a urethane, generation of the enone moiety via a seleno derivative, and, finally, alkylation with the allylic bromide **12** afforded the enantioenriched vinyl halide (−)-**11**. The overall yield from (−)-**18** (six steps) was 27%.

Reductive Heck-type cyclization of (−)-**11**, under the best conditions found in the racemic series (entry 9, Table 2), afforded (−)-**14**, from which the oxidized C-17 was introduced by methoxycarbonylation of the corresponding enolate with methyl cyanoformate (67% yield). The resulting β-keto ester (+)-**19**, which exists in enol form, contains all the strychnine carbons except the two derived from acetate. To complete the



Scheme 8. Enantioselective synthesis of (−)-strychnine. a) 2-$IC_6H_4NO_2$, K_2CO_3, DMSO, 85–90 °C, 72%; b) $BrCH_2CH{=}CH_2$, K_2CO_3, acetone, reflux, 85%; c) toluene, sealed tube, 180–190 °C, 80%; d) O_3, CH_2Cl_2, −78 °C, then (*S*)-$PhCH(CH_3)NH_2\cdot HCl$, $NaBH_3CN$, *i*PrOH, 37%; e) $ClCO_2CHClCH_3$, 135 °C, 72%; f) $HN(SiMe_3)_2$, Me_3SiI, CH_2Cl_2/pentane 1:1, −20 °C; g) PhSeCl, $(PhSe)_2$, THF, 70%; h) O_3, CH_2Cl_2, −78 °C, then *i*Pr_2NH, 72%; i) MeOH, reflux; j) (*Z*)-$BrCH_2CI{=}CHCH_2OTBDMS$ (**12**), K_2CO_3, LiI, CH_3CN, 50 °C, 74%; k) $Pd(OAc)_2$, PPh_3, Et_3N, 90 °C, 53%; l) $LiN(SiMe_3)_2$, HMPA, THF, −78 °C, then $NCCO_2Me$, 67%; m) Zn dust, H_2SO_4, MeOH, reflux, 36%; n) NaH, MeOH, reflux, 72%; o) DIBAL-H, toluene, −40 °C, 65%; p) $CH_2(CO_2H)_2$, Ac_2O, NaOAc, AcOH, 110 °C, 49%.

synthesis of the Wieland–Gumlich aldehyde only the closure of the indoline ring and the reduction of the ester group to an aldehyde remained to be done. The reductive cyclization of the α-(2-nitrophenyl) ketone moiety was satisfactorily accomplished by treatment of (+)-**19** with zinc dust in 10% methanolic sulfuric acid. Under the reaction conditions, that also caused the removal of the TBDMS protecting group, the initially formed anilinoacrylate intermediate undergoes further reduction to an epimeric mixture of esters **20** and **21** (ratio approximately 9:1). This mixture was equilibrated to pure **21**, which has the natural, most stable stereochemistry at C-16, by treatment with NaH in refluxing MeOH. The pentacyclic ester **21**[35] was isolated in 26% overall yield from (+)-**19**. The relative configuration at C-16 in esters **20** and **21** was clearly determined from the vicinal coupling constant between H-15 and H-16, which is larger ($J = 9.9$ Hz) in ester **21**, with the natural H-15/H-16 *cis* strychnine stereochemistry, than in **20** (H-15/H-16 *trans*, $J = 3.7$ Hz).[36] Finally, further adjustment of the oxidation level by partial reduction of ester **21** with DIBAH in toluene at −40 °C afforded the Wieland–Gumlich aldehyde.[37, 38]

Although the conversion of the Wieland–Gumlich aldehyde to strychnine had been reported many years ago[13] and there would therefore seem to be little need to repeat it, we reproduced the described protocol for the sake of completion and thus achieved the enantioselective total synthesis of the natural product. The resulting (−)-strychnine was identical to a natural specimen, as determined by TLC as well as IR, ^1H NMR, and ^{13}C NMR spectroscopy. The $[\alpha]_D^{25}$ value was −119.4 ($c = 0.35$ in $CHCl_3$) [lit[13] $[\alpha]_D^{25} = -139$ ($c = 2.0$ in $CHCl_3$)], which represents 86% *ee*.[39]

In summary, we have completed a short enantioselective synthesis of (−)-strychnine (15 steps from commercially available 1,3-cyclohexanedione in 0.15% overall yield). The synthesis proceeds via the Wieland–Gumlich aldehyde and starts from the prochiral dione **17** (which preforms the A and E rings of strychnine), from which the pyrrolidine, piperidine, and indoline rings are successively built in three well-differentiated phases: i) generation of the first chiral nonracemic intermediate, the 3a-(2-nitrophenyl)octahydroindol-4-one [(−)-**18**], which contains the crucial quaternary C-7 center; ii) closure of the piperidine ring by a reductive Heck-type cyclization that ensures the stereoselective incorporation of the C-20 *E*-configurated double bond; and iii) closure of the indoline ring in an advanced synthetic stage by reductive cyclization of the α-(2-nitrophenyl) ketone moiety. In conjunction with our previous work,[11] the synthesis of strychnine reported here makes evident not only the usefulness of our strategy for the enantioselective synthesis of *Strychnos* alkaloids but also how the use of common synthetic intermediates can provide a flexible access to a large number of structurally related natural products.

Experimental Section

General methods: All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions. All commercially available reagents were used without further purification. TLC was carried out on SiO_2 coated glass plates (silica gel 60 F_{254}, Merck), and the spots were located with UV light, iodoplatinate reagent or 1% aqueous $KMnO_4$. Chromatography refers to flash chromatography and was carried out on SiO_2 (silica gel, SDS, 230–400 mesh ASTM). Unless otherwise noted, drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotatory evaporator. Optical rotations were recorded with a Perkin–Elmer 241 polarimeter. ^1H NMR and ^{13}C NMR spectra were recorded with a Varian 300 or a Varian VXR-500 instrument. Chemical shifts are reported in ppm downfield from Me_4Si. IR spectra were recorded on a Nicolet 205 FT-IR spectrophotometer, and only noteworthy absorptions are listed. Microanalyses and HRMS were performed by Centro de Investigación y Desarrollo (CSIC), Barcelona.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-(trimethylsilyl)-2-butynyl acetate (5a): Tris(trimethylsilyl)aluminum etherate[16b] (11.7 mmol, 37 mL of 0.32 M solution in pentane) was added dropwise to a cooled (−78 °C) solution of 4-[(*tert*-butyldimethylsilyl)oxy]-2-butynal[15] (**4**, 2 g, 11.7 mmol) in Et_2O (20 mL). After the solution was stirred at −78 °C for 1 h, Ac_2O (5.9 mL, 62 mmol), and a catalytic amount of 4-DMAP were added. The mixture was stirred at room temperature for 16 h, poured into an ice-cold saturated aqueous sodium potassium tartrate solution, and extracted with Et_2O. The organic layer was washed with saturated aqueous sodium potassium

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tartrate solution, dried and concentrated, and the residue was purified by chromatography (from hexane to 97:3 hexane/EtOAc) to give **5a** (2.1 g, 57%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.21$ (s, 1H; CHOAc), 4.36 (s, 2H; CH_2O), 2.01 (s, 3H; CH_3), 0.90 (s, 9H; $C(CH_3)_3$), 0.14 (s, 9H; $Si(CH_3)_3$), 0.11 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$ (CO), 86.4 (C), 81.6 (C), 58.2 (CHOAc), 51.8 (CH_2O), 25.7 ($(CH_3)_3$), 20.8 (CH_3), 18.2 (C), −4.0 ($Si(CH_3)_3$), −5.2 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1747$, 1252, 1228, 839 cm^{-1}; $C_{15}H_{30}O_3Si_2$ (314.6) · ¼H_2O: calcd C 56.46, H 9.63; found C 56.20, H 9.49.

1-[(*tert*-Butyldimethylsilyl)oxy]-4-(methoxymethoxy)-4-(trimethylsilyl)-2-butyne (5b): The title compound was obtained analogous to the preparation of **5a** from the reaction of aldehyde **4** (4 g, 23.5 mmol), tris(trimethylsilyl)aluminum etherate (12.1 mmol, 87 mL of 0.14 M solution in pentane), MOMCl (9.3 mL, 122 mmol), and ethyldiisopropylamine (10.5 mL, 61 mmol), and subsequent chromatography (from hexane to 98:2 hexane/EtOAc): **5b** (2.24 g, 30%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 4.92 (d, $J = 6.4$ Hz, 1H; OCH_2O), 4.50 (d, $J = 6.4$ Hz, 1H; OCH_2O), 4.34 (d, $J = 1.8$ Hz, 2H; CH_2O), 4.07 (t, $J = 1.8$ Hz, 1H; CHSi), 3.30 (s, 3H; OCH_3), 0.87 (s, 9H; $C(CH_3)_3$), 0.12 (s, 9H; $Si(CH_3)_3$), 0.08 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 94.8$ (OCH_2O), 86.2 (C), 82.6 (C), 58.5 (CHSi), 55.2 (OCH_3), 51.8 (CH_2O), 25.7 ($(CH_3)_3$), 18.2 (C), −4.0 ($Si(CH_3)_3$), −5.2 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1250$, 1081, 1032, 838 cm^{-1}.

4-Hydroxy-1-(trimethylsilyl)-2-butynyl acetate (6a): A catalytic amount of 10-camphorsulfonic acid was added to a cooled (0 °C) solution of ester **5a** (2 g, 6.5 mmol) in 1:1 CH_2Cl_2/MeOH (50 mL). After the solution was stirred for 1 h at 0 °C and 1 h at room temperature, the solvent was removed in vacuo, and the residue was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The organic layer was dried and concentrated, and the residue was purified by chromatography (from hexane to 3:2 hexane/EtOAc) to give **6a** (0.69 g, 53%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.19$ (s, 1H; CHOAc), 4.32 (s, 2H; CH_2O), 2.09 (s, 3H; CH_3), 1.76 (br s, 1H; OH), 0.14 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.9$ (CO), 86.3 (C), 82.1 (C), 58.2 (CHOAc), 50.7 (CH_2O), 20.7 (CH_3), −4.2 ($Si(CH_3)_3$); IR (film): $\tilde{\nu} = 3600-3200$, 1748, 1251, 1231, 845 cm^{-1}; HRMS: calcd for $C_9H_{16}O_3Si$: 200.0869; found 200.0876; $C_9H_{16}O_3Si$ (200.3) · ¼H_2O: calcd C 52.77, H 8.12; found C 52.38, H 7.89.

4-(Methoxymethoxy)-4-(trimethylsilyl)-2-butynol (6b): The title compound was obtained analogous to the preparation of **6a** from **5b** (2 g, 6.3 mmol) and subsequent chromatography (from hexane to 4:1 hexane/EtOAc): **6b** (0.8 g, 63%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 4.94$ (d, $J =$ 6.4 Hz, 1H; OCH_2O), 4.54 (d, $J = 6.4$ Hz, 1H; OCH_2O), 4.31 (d, $J = 1.9$ Hz, 2H; CH_2O), 4.10 (t, $J = 1.9$ Hz, 1H; CHSi), 3.34 (s, 3H; OCH_3), 1.87 (br s, 1H; OH), 0.15 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 94.8$ (OCH_2O), 86.1 (C), 83.5 (C), 58.6 (CHSi), 55.3 (OCH_3), 51.0 (CH_2O), −4.1 ($Si(CH_3)_3$); IR (film): $\tilde{\nu} = 3600-3200$, 1250, 1089, 1031, 846 cm^{-1}.

4-Iodo-1-(trimethylsilyl)-2-butynyl acetate (7a): Methyltriphenoxyphosphonium iodide (3.39 g, 7.5 mmol) was added to a cooled (0 °C) solution of alcohol **6a** (0.75 g, 3.7 mmol) in DMF (35 mL). After the solution was stirred for 1 h at 0 °C, the reaction was quenched by addition of MeOH (1 mL). The mixture was diluted with Et_2O and washed with saturated aqueous $Na_2S_2O_3$ and brine. The organic layer was dried and concentrated, and the residue was purified by chromatography (from hexane to 9:1 hexane/EtOAc) to give propargylic iodide **7a** (0.95 g, 82%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.10$ (t, $J = 2.4$ Hz, 1H; CHOAc), 3.74 (d, $J = 2.4$ Hz, 2H; CH_2I), 2.05 (s, 3H; CH_3), 0.13 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz): $\delta = 170.5$ (CO), 84.5 (C), 82.7 (C), 58.3 (CHOAc), 20.8 (CH_3), −3.8 ($Si(CH_3)_3$), −17.8 (CH_2I); IR (film): $\tilde{\nu} = 2240$, 1739, 1251, 1229, 845 cm^{-1}; $C_9H_{15}IO_2Si$ (310.2): calcd C 34.85, H 4.87; found C 34.45, H 4.86.

4-Iodo-1-(methoxymethoxy)-1-(trimethylsilyl)-2-butyne (7b): The title compound was obtained analogous to the preparation of **7a** from alcohol **6b** (0.72 g, 3.6 mmol) and subsequent chromatography (from hexane to 97:3 hexane/EtOAc): **7b** (0.92 g, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 4.89 (d, $J = 6.4$ Hz, 1H; OCH_2O), 4.53 (d, $J = 6.5$ Hz, 1H; OCH_2O), 4.06 (t, $J = 2.4$ Hz, 1H; CHSi), 3.78 (d, $J = 2.4$ Hz, 2H; CH_2I), 3.33 (s, 3H; OCH_3), 0.14 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 95.1$ (OCH_2O), 84.3 (C), 58.8 (CHSi), 55.3 (OCH_3), −3.9 ($Si(CH_3)_3$), −17.3 (CH_2I); IR (film): $\tilde{\nu} = 2240$, 1249, 1029 cm^{-1}.

***cis*-1-[4-Acetoxy-4-(trimethylsilyl)-2-butynyl]-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (3a)**: Propargylic iodide **7a** (0.32 g, 1 mmol) and anhydrous K_2CO_3 (0.14 g, 1 mmol) were added to a solution of crude racemic hexahydroindolone **2** · HCl[11e] (0.2 g, 0.68 mmol) in 2-butanone (10 mL). The mixture was heated at reflux for 5 h. The solvent was removed in vacuo, and the residue was partitioned between H_2O and CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was purified by chromatography (from hexane to 1:1 hexane/EtOAc) to give enone **3a** (0.2 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.80$ (d, $J = 8.0$ Hz, 1H; H-3′), 7.65–7.50 (m, 2H; H-5′, H-6′), 7.42 (td, $J = 8.0$, 1.6 Hz, 1H; H-4′), 6.86 (dm, $J = 10.2$ Hz, 1H; H-6), 6.19 (dd, $J = 10.2$, 1.2 Hz, 1H; H-5), 5.13, 5.07 (2t, $J = 2.0$ Hz, 1H; CHSi), 3.63 (dt, $J = 6.3$, 2.2 Hz, 1H; H-7a), 3.59 (m, 2H; H-2), 3.20–3.00 (m, 2H; H-3), 2.81 (dm, $J = 19.3$ Hz, 1H; H-7), 2.60–2.40 (m, 3H; H-7, NCH_2), 2.08, 2.06 (2s, 3H; CH_3CO), 0.08–0.05 (m, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 196.7$ (C-4), 170.3 and 170.2 (COO), 148.7 (C-2′), 146.0 and 145.9 (C-6), 136.8 and 136.6 (C-1′), 132.5 and 132.4 (C-5), 130.1 and 130.0 (C-5′), 127.9 (C-6′), 127.5 (C-4′), 124.8 and 124.7 (C-3′), 81.9 (C), 81.8 (C), 81.7 (C), 81.6 (C), 65.4 and 65.3 (C-7a), 58.5 (C-3a), 57.8 (CHOAc), 49.8 (C-2), 39.7 (CH_2N), 36.4 and 36.1 (C-3), 26.2 and 25.9 (C-7), 20.6 (CH_3), −4.3 ($Si(CH_3)_3$); IR (film): $\tilde{\nu} = 1730$, 1673, 1528, 1367 cm^{-1}; $C_{23}H_{28}N_2O_5Si$ (440.6): calcd C 62.70, H 6.41, N 6.36; found C 62.82, H 6.31, N 6.35.

***cis*-1-[4-(Methoxymethoxy)-4-(trimethylsilyl)-2-butynyl]-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (3b)**: The title compound was obtained analogous to the preparation of **3a** from **2** · HCl (0.3 g, 1 mmol) and propargylic iodide **7b** (0.44 g, 1.5 mmol), and subsequent chromatography (from hexane to 1:1 hexane/EtOAc): enone **3b** (113 mg, 25%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.74$ (dd, $J = 8.0$, 1.5 Hz, 1H; H-3′), 7.58–7.45 (m, 2H; H-5′, H-6′), 7.37 (ddd, $J = 8.0$, 7.0, 1.6 Hz, 1H; H-4′), 6.81 (dm, $J = 10.2$ Hz, 1H; H-6), 6.15 (dm, $J = 10.2$ Hz, 1H; H-5), 4.81, 4.78 (2d, $J =$ 6.4 Hz, 1H; OCH_2O), 4.43, 4.42 (2d, $J = 6.4$ Hz, 1H; OCH_2O), 3.98, 3.96 (2t, $J = 1.9$ Hz, 1H; CHSi), 3.59 (m, 1H; H-7a), 3.55 (m, 2H; H-2), 3.27, 3.26 (2s, 3H; OCH_3), 3.16–2.95 (m, 2H; H-3), 2.76 (dm, $J = 19.2$ Hz, 1H; H-7) 2.52–2.40 (m, 3H; H-7, NCH_2), 0.06–0.03 (m, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.0$ (C-4), 148.0 (C-2′), 146.2 and 146.1 (C-6), 137.1 (C-1′), 132.7 (C-5), 130.2 (C-5′), 128.3 and 128.1 (C-6′), 127.8 (C-4′), 125.1 (C-3′), 94.7 (OCH_2O), 83.1 (C), 81.3 (C), 65.5 (C-7a), 58.8 (C-3a), 58.4 (CHO), 55.3 (CH_3), 50.1 (C-2), 40.0 (CH_2N), 36.8 and 36.6 (C-3), 26.6 and 26.5 (C-7), −4.1 ($SiCH_3$); IR (film): $\tilde{\nu} = 1673$, 1527, 1355 cm^{-1}.

Lewis acid promoted cyclization of 3a: Freshly distilled $BF_3 \cdot Et_2O$ (0.15 mL, 1.2 mmol) was added dropwise to a cooled (0 °C) solution of propargylic silane **3a** (130 mg, 0.3 mmol) in CH_2Cl_2 (15 mL). After the solution was stirred for 22 h at room temperature, the mixture was poured into saturated aqueous Na_2CO_3, and extracted with CH_2Cl_2. The organic layer was dried and concentrated, and the residue was purified by chromatography (from CH_2Cl_2 to 19:1 CH_2Cl_2/MeOH) to give alcohol **8** (68 mg, 57%) and ketone **9** (10 mg, 8%). When the reaction was carried out under the conditions of entry 2, Table 1, compound **10** was also isolated after chromatography.

(4*RS*,6*SR*,7*SR*,10*RS*,12*SR*)-7-Hydroxy-4-(2-nitrophenyl)-8-(trimethylsilyl)-1-azatetracyclo[7.3.1.0^{4,12}.0^{6,10}]tridec-8-en-5-one (8):[40] ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.67$ (dd, $J = 8.0$, 1.5 Hz, 1H; H-12), 7.55 (ddd, $J = 8.3$, 7.0, 1.5 Hz, 1H; H-10), 7.45 (dd, $J = 8.3$, 1.3 Hz, 1H; H-9), 7.32 (ddd, $J = 8.0$, 7.0, 1.3 Hz, 1H; H-11), 5.11 (ddd, $J = 5.3$, 2.0, 1.0 Hz, 1H; H-18), 3.85 (br s, 1H; H-3), 3.78 (ddd, $J = 13.5$, 2.0, 1.0 Hz, 1H; H-21α), 3.65 (td, $J = 13.0$, 6.5 Hz, 1H; H-5α), 3.35 (d, $J = 13.5$ Hz, 1H; H-21β), 3.27 (dd, $J =$ 13.0, 8.5 Hz, 1H; H-5β), 3.09 (t, $J = 5.3$ Hz, 1H; H-16), 3.03 (br s, 1H; H-15), 2.85 (ddd, $J = 15.0$, 3.5, 1.3 Hz, 1H; H-14*pro-R*), 2.71 (ddd, $J = 14.5$, 13.0, 8.5 Hz, 1H; H-6β), 2.20 (dd, $J = 14.5$, 6.5 Hz, 1H; H-6α), 2.16 (ddd, $J = 15.0$, 5.0, 3.0 Hz, 1H; H-14*pro-S*), 0.18 (s, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 213.8$ (C-2), 157.9 (C-19), 148.5 (C-13), 142.8 (C-20), 141.8 (C-8), 133.5 (C-10), 129.6 (C-9), 127.3 (C-11), 124.7 (C-12), 84.1 (C-18), 70.2 (C-3), 63.9 (C-7), 62.2 (C-16), 59.6 (C-5), 51.9 (C-21), 45.1 (C-6), 41.1 (C-15), 21.0 (C-14), 0.1 ($Si(CH_3)_3$); IR (film): $\tilde{\nu} = 3700$, 1689, 1678, 1530, 1363 cm^{-1}; HRMS: calcd for $C_{21}H_{26}N_2O_4Si$ 398.1662; found 398.1654; $C_{21}H_{26}N_2O_4Si$ (398.5) · ½H_2O: calcd C 61.89, H 6.68, N 6.87; found C 61.65, H 6.50, N 6.49.

(1*RS*,2*SR*,7*RS*,8*SR*)-2-(2-Acetoxyacetyl)-7-(2-nitrophenyl)-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one (9):[40] ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54-$ 7.47 (m, 2H; H-10, H-12), 7.38 (td, $J = 7.7$, 1.3 Hz, 1H; H-11), 7.22 (dd, $J =$ 8.0, 1.5 Hz, 1H; H-9), 4.80 (d, $J = 16.8$ Hz, 1H; CH_2O), 4.57 (d, $J = 16.8$ Hz, 1H; CH_2O), 3.27–2.94 (m; 5H), 3.83 (t, $J = 3.0$ Hz, 1H; H-3), 2.75 (br s, 1H; H-15), 2.67 (dt, $J = 18.0$, 2.0 Hz, 1H; H-16), 2.61–2.40 (m; 3H), 2.38

(dt, $J = 14.0$, 3.0 Hz, 1H; H-14), 2.20 (dm, $J = 14.0$ Hz, 1H; H-14), 2.17 (s, 3H; CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 211.5$ (C-2), 202.6 (C-19), 170.1 (COO), 150.8 (C-13), 134.0 (C-8), 131.8 (C-10), 129.8 (C-9), 128.0 (C-11), 125.4 (C-12), 66.8 (C-18), 64.9 (C-3), 62.0 (C-7), 54.8 (C-5), 48.5 (C-20), 45.2 (C-21), 41.9 (C-16), 39.4 (C-6), 29.6 (C-15), 26.6 (C-14), 20.3 (CH_3); IR (film): $\tilde{\nu} = 1750$, 1725, 1699, 1531, 1366 cm^{-1}.

(4*RS*,6*SR*,7*SR*,8*RS*,10*SR*)-7-[(*E*)-2-Acetoxy-1-(trimethylsilyl)vinyl]-4-(2-nitrophenyl)-1-azatetracyclo[5.3.1.0^{4,10}.0^{6,8}]undecan-5-one (10):[40] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (dd, $J = 8.0$, 1.4 Hz, 1H; H-12), 7.55 (ddd, $J =$ 8.0, 7.0, 1.4 Hz, 1H; H-10), 7.40 (d, $J = 8.0$ Hz, 1H; H-9), 7.35 (ddd, $J = 8.0$, 7.0, 1.4 Hz, 1H; H-11), 7.14 (s, 1H; H-18), 3.57 (d, $J = 14.0$ Hz, 1H; H-21α), 3.54 (s, 1H; H-3), 3.25 (ddd, $J = 12.2$, 9.7, 7.7 Hz, 1H; H-5α), 3.01 (ddd, $J =$ 12.2, 7.5, 3.0 Hz, 1H; H-5β), 2.89 (d, $J = 14.0$ Hz, 1H; H-21β), 2.70–2.60 (m, 2H; H-6β, H-14), 2.55–2.45 (m, 2H; H-6α, H-14), 2.23–2.16 (masked, 1H; H-15), 2.18 (s, 3H; $COCH_3$), 1.96 (d, $J = 7.9$ Hz, 1H; H-16), 0.22–0.18 (m, 9H; $Si(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 209.6$ (C-2), 167.4 (COO), 150.2 (C-13), 142.5 (C-18), 136.4 (C-8), 132.4 (C-10), 130.3 (C-9), 127.5 (C-11), 124.6 (C-12), 122.8 (C-19), 68.2 (C-3), 60.3 (C-7), 57.9 (C-5), 51.8 (C-21), 44.0 (C-6), 39.2 (C-16), 35.6 (C-20), 24.7 (C-15), 20.8 (CH_3), 18.8 (C-14), −0.31 ($Si(CH_3)_3$); IR (film): $\tilde{\nu} = 1762$, 1688, 1681, 1533, 1366 cm^{-1}; HRMS: calcd for $C_{23}H_{28}N_2O_5Si$ 440.1768; found 440.1777; $C_{23}H_{28}N_2O_5Si$ (440.6) · 1.75 H_2O: calcd C 58.52, H 6.73, N 5.93; found C 58.45, H 6.33, N 5.89.

(*Z*)-1-Bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodo-2-butene (12): A solution of 4-(tetrahydropyran-2-yloxy)-2-butynol[41] (5.38 g, 31.6 mmol) in Et_2O (20 mL) was added dropwise to a cooled (0 °C) solution of RedAl (53.7 mmol, 15.5 g of 70% solution in toluene) in Et_2O (40 mL). The resulting solution was slowly warmed to room temperature. The excess of RedAl was destroyed by addition of AcOEt (1 mL). The mixture was cooled to −78 °C, a solution of I_2 (10 g, 39.4 mmol) in THF (20 mL) was added dropwise, and the resulting solution was allowed to warm slowly to room temperature. The mixture was poured into saturated aqueous sodium potassium tartrate solution and extracted with Et_2O. The organic extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over K_2CO_3/Na_2SO_4, and concentrated. Purification by chromatography (from hexane to 1:1 hexane/EtOAc) yielded (*Z*)-3-iodo-4-(tetrahydropyran-2-yloxy)-2-butenol (4.24 g, 45%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.26$ (t, $J = 5.7$ Hz, 1H; =CH), 4.70 (m; 1H), 4.33 (d, $J = 11.5$ Hz, 1H; CH_2OTHP), 4.27 (d, $J =$ 5.7 Hz, 2H; CH_2O), 4.21 (d, $J = 11.5$ Hz, 1H; CH_2OTHP), 3.90 (m; 1H), 3.55 (m; 1H), 2.00–1.50 (m; 6H).

A solution of this alcohol (11.8 g, 39.6 mmol), TBDMSCl (13.1 g, 87 mmol), and imidazole (5.4 g, 79 mmol) in DMF (75 mL) was stirred at room temperature for 1 h. The mixture was diluted with Et_2O and washed with 3% aqueous Na_2CO_3, saturated aqueous NH_4Cl, and water. The organic extracts were dried and concentrated to give (*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodo-1-(tetrahydropyran-2-yloxy)-2-butene (16.3 g, quantitative), which was used without purification. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.18$ (t, $J = 5.2$ Hz, 1H; =CH), 4.69 (t, $J = 3.5$ Hz; 1H), 4.32 (d, $J =$ 13.2 Hz, 1H; CH_2OTHP), 4.27 (d, $J = 5.2$ Hz, 2H; $CH_2OTBDMS$), 4.20 (d, $J = 13.2$ Hz, 1H; CH_2OTHP), 3.54 (m; 1H), 3.89 (m, 1H), 2.00–1.50 (m; 6H), 0.91 (s, 9H; $C(CH_3)_3$), 0.09 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 137.0$ (=CH), 101.4 (=CI), 96.8 (CH), 74.0 (CH_2OTHP), 67.6 (CH_2OSi), 61.8 (CH_2), 30.2 (CH_2), 25.8 (($CH_3)_3$), 25.3 (CH_2), 18.9 (CH_2), 18.1 (C), −5.3 ($Si(CH_3)_2$).

A solution of this tetrahydropyranyl ether (7.98 g, 19.4 mmol) and $MgBr_2 \cdot Et_2O$ (25 g, 96.8 mmol) in Et_2O (250 mL) was stirred at room temperature for 24 h. The mixture was poured into water and extracted with Et_2O (3 × 150 mL) and CH_2Cl_2 (150 mL). The combined organic extracts were dried and concentrated to give (*Z*)-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodo-2-butenol (6.35 g, quantitative), which was used without purification. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.17$ (tt, $J = 5.1$, 1.2 Hz, 1H; =CH), 4.29–4.23 (m; 3H), 2.15 (br s, 1H; OH), 0.91 (s, 9H; $C(CH_3)_3$), 0.09 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 135.5$ (=CH), 105.6 (=CI), 71.1 (CH_2OH), 67.6 (CH_2OSi), 25.9 (($CH_3)_3$), 18.3 (C), −5.2 ($Si(CH_3)_2$).

Triphenylphosphine (6.1 g, 23.2 mmol) and *N*-bromosuccinimide (NBS) (4.8 g, 27 mmol) were added to a cooled (−30 °C) solution of this allylic alcohol (6.35 g, 19.4 mmol) in CH_2Cl_2 (300 mL). The mixture was stirred at this temperature for 2 h, diluted with Et_2O, and washed with saturated aqueous $NaHCO_3$ and brine. The organic extracts were dried, concentrated, and then taken up with hexanes. Triphenylphosphine oxide was removed by filtration, and the filtrate was evaporated to give an oil, which was purified by chromatography (from hexane to 49:1 hexane/EtOAc) to yield (*Z*)-1-bromo-4-[(*tert*-butyldimethylsilyl)oxy]-2-iodo-2-butene (**12**, 3.75 g, 50%).[5b] ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.27$ (t, $J = 5.2$ Hz, 1H; =CH), 4.32 (s, 2H; CH_2Br), 4.28 (d, $J = 5.1$ Hz, 2H; CH_2OSi), 0.90 (s, 9H; $C(CH_3)_3$), 0.09 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 140.5$ (=CH), 98.7 (=CI), 68.0 (CH_2OSi), 42.3 (CH_2Br), 25.8 (($CH_3)_3$), 18.2 (C), −5.2 ($Si(CH_3)_2$).

(3a*R*,7a*S*)-*N*-[(*S*)-α-Methylbenzyl]-3a-(2-nitrophenyl)octahydroindol-4-one [(−)-18]: This compound was prepared following the previously reported procedure,[11e] by ozonolysis of 2-allyl-2-(2-nitrophenyl)-1,3-cyclohexanedione (**17**) and then reaction of the resulting diketo aldehyde with (*S*)-α-methylbenzylamine (96% *ee*) and $NaBH_3CN$. A 97:3 mixture (determined by HPLC analysis) of *cis*-octahydroindolone (−)-**18** and the other *cis* diastereomer was obtained in 37% yield after column chromatography. A second eluate afforded a 3:1 mixture of the two *trans*-octahydroindolones in 8% yield.

(3a*R*,7a*S*)-1-{(*Z*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-iodo-2-butenyl}-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one [(−)-11]: Chiral non-racemic tertiary amine (−)-**18** was converted to (3a*R*,7a*S*)-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one hydrochloride as previously reported.[11e] To a solution of this crude hydrochloride (0.4 g, 1.36 mmol) in CH_3CN (20 mL) were added anhydrous K_2CO_3 (0.38 g, 2.74 mmol), allylic bromide **12** (1.07 g, 2.74 mmol), and a catalytic amount of LiI. The mixture was stirred at 50 °C for 3 h. The solvent was removed in vacuo, and the residue was partitioned between H_2O and CH_2Cl_2. The organic layer was washed with water, dried, and concentrated. Purification by chromatography (CH_2Cl_2) afforded enone (−)-**11** (576 mg, 74%). $[\alpha]_D^{20} = -113.4$ ($c = 1.5$ in MeOH); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (dd, $J = 8.0$, 1.2 Hz, 1H; H-3′), 7.65–7.53 (m, 2H; H-5′, H-6′), 7.41 (td, $J = 8.0$, 1.8 Hz, 1H; H-4′), 6.86 (ddd, $J = 10.2$, 4.9, 3.6 Hz, 1H; H-6), 6.15 (ddt, $J = 10.2$, 2.5, 1.9 Hz, 1H; H-5), 5.98 (t, $J = 5.0$ Hz, 1H; =CH), 4.19 (d, $J = 5.0$ Hz, 2H; CH_2O), 3.77 (t, $J = 6.6$ Hz, 1H; H-7a), 3.35 (s, 2H; NCH_2), 3.11 (dt, $J =$ 10.0, 7.5 Hz, 1H; H-2), 2.92 (td, $J = 10.0$, 3.5 Hz, 1H; H-2), 2.65 (dddd, $J =$ 19.4, 6.6, 4.9, 1.7 Hz, 1H; H-7), 2.60–2.40 (m, 2H; H-3, H-7), 2.37 (ddd, $J =$ 14.5, 10.0, 7.5 Hz, 1H; H-3), 0.90 (s, 9H; $C(CH_3)_3$), 0.07 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.3$ (C-4), 148.2 (C-2′), 145.3 (C-6), 137.6 (C-1′), 136.6 (=CH), 132.5 (C-5′), 131.3 (C-5), 127.8 (C-4′ and C-6′), 125.2 (C-3′), 104.6 (=CI), 67.8 (CH_2O), 66.0 (C-7a), 62.2 (CH_2N), 59.4 (C-3a), 49.2 (C-2), 34.4 (C-3), 25.8 (($CH_3)_3$), 25.2 (C-7), 18.2 (C), −5.2 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1673$, 1528, 1352 cm^{-1}; $C_{24}H_{33}IN_2OSi$ (520.5): calcd C 50.70, H 5.85, N 4.93; found C 50.74, H 5.97, N 4.92.

Palladium-promoted tandem cyclization-quenching of vinyl iodide 11: Attempted tandem cyclization-quenching processes were carried out from racemic **11** (prepared as above from racemic **2**) under the experimental conditions summarized in Table 2.

Methyl 4-[(*tert*-butyldimethylsilyl)oxy]-2-{[*cis*-3a-(2-nitrophenyl)-4-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indol-1-yl]methyl}-2-(*Z*)-butenoate (13): ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (dd, $J = 8.0$, 1.5 Hz, 1H; H-3′), 7.57 (td, $J = 8.0$, 1.5 Hz, 1H; H-5′), 7.47 (dd, $J = 8.0$, 1.5 Hz, 1H; H-6′), 7.40 (td, $J = 8.0$, 1.5 Hz, 1H; H-4′), 6.86 (dt, $J = 10.2$, 4.5 Hz, 1H; H-6), 6.13 (dd, $J =$ 10.2, 2.0 Hz, 1H; H-5), 6.06 (t, $J = 4.9$ Hz, 1H; =CH), 4.51 (d, $J = 4.9$ Hz, 2H; CH_2OSi), 3.70 (t, $J = 6.5$ Hz, 1H; H-7a), 3.49 (s, 3H; OCH_3), 3.38–3.31 (m, 2H; NCH_2), 3.06 (dt, $J = 9.5$, 7.8 Hz, 1H; H-2), 2.90 (td, $J = 9.5$, 3.4 Hz, 1H; H-2), 2.68 (dddd, $J = 19.1$, 6.5, 4.5, 1.8 Hz, 1H; H-7), 2.55–2.42 (m, 2H; H-3, H-7), 2.35 (ddd, $J = 14.2$, 9.5, 7.8 Hz, 1H; H-3), 0.89 (s, 9H; $C(CH_3)_3$), 0.05 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.4$ (C-4), 167.0 (COO), 148.3 (C-2′), 145.7 (C-6), 144.8 (=CH), 137.8 (C-1′), 132.4 (C-5′), 130.7 (C-5), 127.8 and 127.7 (C-4′ and C-6′), 125.2 (C-3′), 67.0 (C-7a), 61.6 (CH_2O), 59.3 (C-3a), 53.5 (CH_2N), 51.3 (OCH_3), 49.8 (C-2), 34.8 (C-3), 25.9 (($CH_3)_3$), 25.2 (C-7), 18.2 (C), −5.3 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1715$, 1673, 1527, 1355 cm^{-1}; HRMS: calcd for $C_{26}H_{36}N_2O_6Si$ 500.2357; found 500.2343.

***cis*-1-{(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-vinyl-2-butenyl}-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (15)**: ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.86$ (dd, $J = 8.0$, 1.4 Hz, 1H; H-3′), 7.55 (td, $J = 8.0$, 1.4 Hz, 1H; H-5′), 7.47 (dd, $J = 8.0$, 1.4 Hz, 1H; H-6′), 7.37 (td, $J = 8.0$, 1.4 Hz, 1H; H-4′), 6.86 (ddd, $J = 10.1$, 4.7, 3.6 Hz, 1H; H-6), 6.32 (dd, $J = 17.4$, 11.2 Hz, 1H; H-*gem*), 6.13 (ddd, $J = 10.1$, 2.4, 1.9 Hz, 1H; H-5), 5.54 (t, $J = 6.0$ Hz, 1H; =CH), 5.05 (dd, $J = 17.4$, 1.5 Hz, 1H; H-*cis*), 4.87 (dt, $J = 11.2$, 1.5 Hz,

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1H; H-*trans*), 4.30 (d, $J = 6.0$ Hz, 2H; CH_2OSi), 3.68 (t, $J = 6.6$ Hz, 1H; H-7a), 3.33 (d, $J = 13.0$ Hz, 1H; CHN), 3.21 (d, $J = 13.0$ Hz, 1H; CHN), 3.02 (dt, $J = 9.7$, 8.2 Hz, 1H; H-2), 2.85 (td, $J = 9.7$, 3.5 Hz, 1H; H-2), 2.66 (dddd, $J = 19.4$, 6.8, 4.8, 1.8 Hz, 1H; H-7), 2.55–2.42 (m, 2H; H-3, H-7), 2.41–2.28 (m, 1H; H-3), 0.89 (s, 9H; $C(CH_3)_3$), 0.05 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.6$ (C-4), 148.3 (C-2′), 145.5 (C-6), 137.8 (C-1′), 133.6 (C), 132.3 (C-5′), 131.6 (CH), 131.0 (CH), 127.8 (CH), 127.6 (CH), 127.5 (CH), 125.1 (C-3′), 116.0 (=CH_2), 66.4 (C-7a), 59.5 (CH_2O), 54.9 (CH_2N), 49.5 (C-2), 34.5 (C-3), 25.9 ($(CH_3)_3$), 24.4 (C-7), 18.2 (C), −5.2 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1673$, 1527, 1353 cm^{-1}; HRMS: calcd for $C_{26}H_{36}N_2O_4Si$ 468.2455; found 468.2444.

***cis*-1-{(*E*)-4-[(*tert*-Butyldimethylsilyl)oxy]-2-butenyl}-3a-(2-nitrophenyl)-1,2,3,3a,7,7a-hexahydroindol-4-one (16)**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.85 (dd, $J = 8.0$, 1.5 Hz, 1H; H-3′), 7.59 (td, $J = 8.0$, 1.5 Hz, 1H; H-5′), 7.52 (dd, $J = 8.0$, 1.5 Hz, 1H; H-6′), 7.41 (td, $J = 8.0$, 1.5 Hz, 1H; H-4′), 6.86 (dt, $J = 10.2$, 4.2 Hz, 1H; H-6), 6.15 (dt, $J = 10.2$, 2.1 Hz, 1H; H-5), 5.70–5.50 (m, 2H; =CH), 4.11 (dd, $J = 4.2$, 1.0 Hz, 2H; CH_2OSi), 3.61 (t, $J = 6.0$ Hz, 1H; H-7a), 3.22 (dd, $J = 14.0$, 5.0 Hz, 1H; CHN), 3.07 (dd, $J = 14.0$, 5.5 Hz, 1H; CHN), 3.02–2.93 (m, 2H; H-2), 2.68 (dddd, $J = 19.3$, 6.5, 4.3, 2.0 Hz, 1H; H-7), 2.55–2.25 (m, 3H; H-3, H-7), 0.88 (s, 9H; $C(CH_3)_3$), 0.04 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 197.5$ (C-4), 148.5 (C-2′), 146.0 (C-6), 137.8 (C-1′), 132.5 (C-5′), 131.9 (CH), 130.6 (CH), 127.9 (CH), 127.7 (CH), 127.0 (CH), 125.2 (C-3′), 66.7 (C-7a), 63.2 (CH_2O), 59.3 (C-3a), 53.5 (CH_2N), 50.5 (C-2), 35.2 (C-3), 25.9 ($(CH_3)_3$), 25.8 (C-7), 18.2 (C), −5.2 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1673$, 1527, 1355 cm^{-1}; HRMS: calcd for $C_{24}H_{34}N_2O_4Si$ 442.2267; found 442.2288.

(1*R*,7*R*,8*S*)-2-{(*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]ethylidene}-7-(2-nitrophenyl)-4-azatricyclo[5.2.2.0^{4,8}]undecan-11-one [(−)-14]: $Pd(OAc)_2$ (15 mg, 0.066 mmol) and triphenylphosphine (34 mg, 0.13 mmol) were added to a solution of vinyl iodide (−)-**11** (125 mg, 0.22 mmol) in Et_3N (10 mL) at 90 °C. The solution was stirred at this temperature for 1.5 h. The mixture was diluted with Et_2O and washed with saturated aqueous Na_2CO_3 and water. The organic layer was concentrated and purified by chromatography (from CH_2Cl_2 to 98:2 CH_2Cl_2/MeOH) to give (−)-**14** (52 mg, 53%). $[\alpha]_D^{20} = -19.4$ ($c = 0.8$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$):[40] $\delta = 7.49$ (m; 2H), 7.38 (m; 2H), 5.48 (t, $J = 6.3$ Hz, 1H; =CH), 4.19 (d, $J = 6.3$ Hz, 2H; OCH_2), 3.93 (br s, 1H; H-3), 3.45 (d, $J = 14.6$ Hz, 1H; H-21eq), 3.27 (m, 1H; H-15), 3.19 (dt, $J = 11.0$, 7.5 Hz, 1H; H-5α), 3.01 (dt, $J = 14.0$, 7.5 Hz, 1H; H-5β), 3.01 (d, $J = 14.6$ Hz, 1H; H-21ax), 2.88 (ddd, $J = 11.0$, 7.5, 3.6 Hz, 1H; H-6β), 2.71 (dd, $J = 17.4$, 6.4 Hz, 1H; H-16ax), 2.52 (dt, $J =$ 17.4, 2.1 Hz, 1H; H-16eq), 2.41–2.31 (m, 1H; H-6α), 2.37 (d m, $J = 14.0$ Hz, 1H; H-14*pro-R*), 2.18 (ddd, $J = 14.0$, 3.5, 2.4 Hz, 1H; H-14*pro-S*), 0.89 (m, 9H; $C(CH_3)_3$), 0.06 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 211.1 (C-2), 150.8 (C-13), 138.2 (C-20), 133.4 (C-8), 131.9 (CH), 129.4 (CH), 128.0 (CH), 125.2 (CH), 125.1 (C-19), 65.3 (C-3), 62.2 (C-7), 58.8 (C-18), 54.3 (C-21), 53.7 (C-5), 46.1 (C-16), 39.2 (C-6), 31.0 (C-15), 26.2 (C-14), 25.9 ($(CH_3)_3$), 18.3 (C), −5.1 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1704$, 1532, 1364 cm^{-1}; HRMS: calcd for $C_{24}H_{34}N_2O_4Si$ 442.2281; found 442.2288; $C_{24}H_{34}N_2O_4Si$ (442.6): calcd C 65.13, H 7.74, N 6.33; found C 64.90, H 7.95, N 6.23.

Methyl (1*S*,7*R*,8*S*)-2-{(*E*)-2-[(*tert*-butyldimethylsilyl)oxy]ethylidene}-7-(2-nitrophenyl)-11-oxo-4-azatricyclo[5.2.2.0^{4,8}]undecan-10-carboxylate [(+)-19]: Hexamethylphosphoric triamide (HMPA) (0.34 mL, 1.97 mmol) and a solution of ketone (−)-**14** (174 mg, 0.39 mmol) in THF (10 mL) were added to a cooled (−78 °C) solution of LiHMDS (1.2 mmol, 1.2 mL of 1M solution in THF) in THF (20 mL). After the solution was stirred for 30 min at −78 °C, the bath was removed, methyl cyanoformate (125 μL, 1.57 mmol) was added, and the mixture was stirred at room temperature for an additional 4 h. The reaction was quenched by addition of saturated aqueous NH_4Cl (20 mL) and the resulting solution was extracted with Et_2O. The organic layer was washed with brine, dried, and concentrated. The residue was purified by chromatography (from CH_2Cl_2 to 97:3 CH_2Cl_2/MeOH) to give ester (+)-**19** (enol form, 122 mg, 62%, 67% based on the consumed starting ketone) and unreacted ketone (−)-**14** (15 mg, 8%). $[\alpha]_D^{20} = +226.4$ ($c = 0.5$ in MeOH); ^{1}H NMR (300 MHz, $CDCl_3$):[40] $\delta = 12.5$ (br s, 1H; OH), 7.53–7.45 (m; 2H), 7.40–7.32 (m; 2H), 5.49 (td, $J = 6.3$, 1.3 Hz, 1H; =CH), 4.43 (ddd, $J = 12.9$, 6.3, 1.2 Hz, 1H; H-18), 4.30 (ddd, $J = 12.9$, 6.3, 1.9 Hz, 1H; H-18), 3.84–3.76 (m, 2H; H-3, H-15), 3.80 (s, 3H; OCH_3), 3.30 (d, $J = 12.8$ Hz, 1H; H-21eq), 3.17 (d, $J = 12.8$ Hz, 1H; H-21ax), 3.25–3.14 (m, 1H; H-5α), 2.97 (dd, $J = 12.5$, 7.9 Hz, 1H; H-5β), 2.80 (ddd, $J = 15.4$, 10.7, 7.9 Hz, 1H; H-6β), 2.39 (dd, $J = 15.4$, 6.8 Hz, 1H; H-6α), 2.09 (ddd, $J = 13.4$, 3.6, 2.5 Hz, 1H; H-14*pro-R*), 1.93 (ddd, $J = 13.4$, 3.8, 2.8 Hz, 1H; H-14*pro-S*), 0.91 (m, 9H; $C(CH_3)_3$), 0.10 (s, 6H; $Si(CH_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.3$ and 172.0 (C-2 and C-17), 150.7 (C-13), 135.8 (C-20), 134.5 (C-8), 131.9 (CH), 131.1 (CH), 127.6 (CH), 124.7 (CH), 124.1 (C-19), 101.7 (C-16), 66.6 (C-3), 59.2 (C-18), 55.9 (C-21), 55.2 (C-7), 54.0 (C-5), 52.1 (OCH_3), 37.5 (C-6), 28.7 (C-15), 26.0 ($(CH_3)_3$), 25.2 (C-14), 18.4 (C), −5.0 ($Si(CH_3)_2$); IR (film): $\tilde{\nu} = 1651$, 1610, 1531, 1363 cm^{-1}; HRMS: calcd for $C_{26}H_{36}N_2O_6Si$ 500.2343; found 500.2363; $C_{26}H_{36}N_2O_6Si$ (500.7) · ½H_2O: calcd C 61.27, H 5.50, N 7.31; found C 61.45, H 5.83, N 7.06.

Methyl (19*E*)-18-hydroxy-19,20-didehydro-17-curanoate (21): Zn dust (25 g) was added to a solution of ester (+)-**19** (185 mg, 0.37 mmol) in 9:1 H_2SO_4/MeOH (50 mL) and the resulting mixture was heated at reflux for 2 h. After cooling to room temperature, the mixture was filtered and the filtrate was concentrated. The resulting residue was diluted with water and treated with saturated aqueous Na_2CO_3 until turbid. The resulting mixture was further basified with NH_4OH and extracted with EtOAc (3 × 50 mL). The aqueous layer was neutralized with 1N HCl and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were dried and concentrated to give a residue. Chromatography (from CH_2Cl_2 to 7:3 CH_2Cl_2/MeOH) afforded an epimeric mixture of esters **20** and **21** (9:1 ratio, 45 mg, 36%). **20**: ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.13–7.04$ (m, 2H; H-9, H-11), 6.81 (t, $J = 7.5$ Hz, 1H; H-10), 6.63 (d, $J = 8.0$ Hz, 1H; H-12), 5.55 (t, $J = 7.0$ Hz, 1H; H-19), 4.25 (dd, $J = 12.5$, 7.0 Hz, 1H; H-18), 4.17 (m, 2H; H-2, NH), 4.16 (dd, $J = 12.5$, 7.0 Hz, 1H; H-18), 3.88–3.74 (m, 1H; H-15), 3.81 (s, 3H; OCH_3), 3.67 (d, $J = 15.2$ Hz, 1H; H-21), 3.61 (br d, $J = 3.0$ Hz, 1H; H-3), 3.32 (d, $J = 15.2$ Hz, 1H; H-21), 3.34–3.23 (m, 1H; H-5), 3.02 (dt, $J = 11.1$, 6.8 Hz, 1H; H-5), 2.72 (t, $J = 3.7$ Hz, 1H; H-16), 2.60 (br s, 1H; OH), 2.48 (td, $J = 13.5$, 6.8 Hz, 1H; H-6), 2.30 (ddd, $J = 14.0$, 3.7, 1.4 Hz, 1H; H-14), 2.13 (dt, $J = 13.5$, 6.8 Hz, 1H; H-6), 1.73 (ddd, $J = 14.0$, 3.7, 3.0 Hz, 1H; H-14).

A solution of esters **20** and **21** (45 mg, 0.13 mmol) in MeOH (5 mL) was added to a solution of sodium hydride (55%, 45 mg) in MeOH (10 mL). The resulting mixture was heated at reflux for 5 h. To reesterify any acid resulting from adventitious hydrolysis, 18% HCl/MeOH (2 mL) was added and the resulting solution was heated at reflux for 12 h. After cooling to room temperature, the mixture was concentrated, basified with 10% aqueous Na_2CO_3, and extracted with EtOAc. The organic layer was dried and concentrated to give a residue. Chromatography (from CH_2Cl_2 to 7:3 CH_2Cl_2/MeOH) afforded ester **21** (32 mg, 72%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$ (td, $J = 7.6$, 1.2 Hz, 1H; H-11), 7.05 (d, $J = 7.6$ Hz, 1H; H-9), 6.77 (td, $J = 7.6$, 1.0 Hz, 1H; H-10), 6.64 (d, $J = 7.6$ Hz, 1H; H-12), 5.68 (td, $J = 7.2$, 1.0 Hz, 1H; H-19), 4.25 (br s, 1H; NH), 4.09 (ddd, $J = 7.2$, 3.8, 1.0 Hz, 2H; H-18), 3.93 (d, $J = 9.9$ Hz, 1H; H-2), 3.76 (s, 3H; OCH_3), 3.54 (t, $J = 3.1$ Hz, 1H; H-3), 3.53 (d, $J = 14.8$ Hz, 1H; H-21), 3.26 (m, 1H; H-15), 3.18 (ddd, $J = 12.2$, 10.0, 6.9 Hz, 1H; H-5), 3.09 (d, $J = 14.8$ Hz, 1H; H-21), 2.85 (ddd, $J = 12.2$, 8.5, 4.1 Hz, 1H; H-5), 2.63–2.50 (m, 1H; H-6), 2.57 (dd, $J = 9.9$, 3.9 Hz, 1H; H-16), 2.08 (dt, $J = 13.5$, 3.6 Hz, 1H; H-14), 2.0 (br s, 1H; OH), 1.95–1.66 (m, 2H; H-14, H-6); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 174.1$ (C-17), 148.5 (C-13), 137.1 (C-20), 132.1 (C-8), 128.1 (C-11), 126.4 (C-19), 121.9 (C-9), 119.1 (C-10), 109.5 (C-12), 66.4 (C-2), 60.8 (C-3), 57.9 (C-18), 57.7 (C-21), 53.8 (C-5), 53.5 (C-7), 52.9 (C-16), 52.3 (OCH_3), 42.1 (C-6), 30.2 (C-15), 28.3 (C-14).

Strychnine (1): DIBAL-H (0.44 mmol, 0.44 mL of 1M solution in hexane) was added dropwise to a cooled (−40 °C) solution of ester **21** (40 mg, 0.12 mmol) in toluene (7 mL). After 25 min at this temperature, the reaction was quenched by addition of EtOAc (1 mL), the cooling bath was removed, and 1N HCl (2 mL) was added. The resulting mixture was stirred at room temperature for 16 h. Concentrated NH_4OH was added, and the mixture was extracted with EtOAc. The organic extracts were dried and concentrated to give a residue (40 mg, 65%) in which the main product was the Wieland–Gumlich aldehyde.[37]

NaOAc (200 mg, 2.4 mmol), malonic acid (200 mg, 1.9 mmol), and Ac_2O (40 mg, 0.4 mmol) were added to a solution of this crude product in acetic acid (1.5 mL). The mixture was heated at 110 °C for 2 h. After cooling to room temperature, the mixture was diluted with water, basified with aqueous 50% NaOH, and extracted with EtOAc. The organic extracts were dried and concentrated, and the residue was purified by chromatography (from CH_2Cl_2 to CH_2Cl_2/MeOH 9:1) to give strychnine (12.5 mg, 49%), which was identical with an authentic sample by comparison of the ^{1}H NMR, ^{13}C NMR, TLC data. $[\alpha]_D^{20} = -119.4$ ($c = 0.35$ in $CHCl_3$); lit[13] $[\alpha]_D^{20} = -139$ ($c = 2.0$ in $CHCl_3$).

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[35] This ester is also an intermediate in the Overman synthesis of strychnine.[6c]

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[36] Similar trends are observed in related esters embodying rings ABCE[36a] and ABCDE[36b] of *Strychnos* alkaloids. a) M.-L. Bennasar, M. Alvarez, R. Lavilla, E. Zulaica, J. Bosch, *J. Org. Chem.* **1990**, *55*, 1156–1168; b) see ref. [6a].
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[38] Starting from racemic **14** we also completed the synthesis of racemic Wieland–Gumlich aldehyde.
[39] This *ee* value is in agreement with the purity of (−)-**18** and α-(*S*)-methylbenzylamine (96% *ee*) and is very similar to that obtained (89% *ee*) in our enantioselective synthesis of (−)-tubifolidine from the same azabicyclo (−)-**18**.[11e]
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