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Palladium-catalyzed oxidative cyclization in alkaloid synthesis: total syntheses of (±)-*cis*- and *trans*-195A

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ABSTRACT

Total syntheses of (±)-*cis*-195A (**1**) and (±)-*trans*-195A (**16**) have been accomplished by a combination of palladium-catalyzed oxidative cyclization and Beckmann rearrangement as key reactions.

Recently, we developed a palladium-catalyzed oxidative cyclization[1] of olefinic keto and lactone esters as an alternative method of the palladium-catalyzed cycloalkenylation for the construction of highly functionalized polycyclic compounds.[2] As an extension of our earlier work, we investigated the application of this catalytic cyclization process in the synthesis of *cis*-195A (**1**), a member of the decahydroquinoline class of dendrobatid alkaloids.

cis-195A (**1**) was originally isolated in 1969 from the skin extracts of *Dendrobates pumilio*, a brightly colored Panamanian poison arrow frog.[3] *cis*-195A (**1**) has been an attractive and challenging target in organic synthesis because of its intriguing pharmacological properties and unique structure.[4]

The retrosynthetic analysis of *cis*-195A (**1**) is outlined in Scheme 1. The transformation of lactam **2** into *cis*-195A (**1**) has been reported by Oppolzer et al.[5] Therefore, we focused on the stereoselective construction of bicyclic lactam **2**. We anticipated that the Beckmann rearrangement of oxime **3** would proceed regioselectively to afford **2**. We believed that **3** would be synthesized by a series of functional group manipulations of *exo*-olefin **4**, which would be accessed from a palladium-catalyzed oxidative cyclization of olefinic keto ester **5**. Finally, *trans*-substituted cyclohexanone **5** would be stereoselectively obtained from **6** by employing a tandem Michael reaction-carbomethoxylation reaction.

Our approach begins with the synthesis of *exo*-olefin **4** by the route depicted in Scheme 2. Conjugate addition of homoallyl magnesium bromide followed by quenching with methyl cyanoformate gave rise to 3,4-*trans*-disubstituted cyclohexanone derivative **5** as a 10:1 diastereomeric mixture of esters in 95% yield.[6] Next, the palladium-catalyzed oxidative cyclization of **5** was performed in the presence of 10 mol % of $Pd(OAc)_2$ to furnish the desired *exo*-olefin **4**[7] in 78% yield together with *endo*-olefin **7** (14%) and cyclohexenone derivative **8** (3%). After the separation of the mixture using silica gel column chromatography, *exo*-olefin **4** was subjected to a hydride reduction followed by tosylation to afford tosylate **9**[7] in 69% overall yield. Reduction of **4** with $NaBH_4$ in the absence of $CeCl_3{\cdot}7H_2O$ was found to decrease the yield of the undesired corresponding alcohol. Ozonolysis of **9** and reductive workup afforded keto tosylate **10**[7] in 79% yield. The structure of **10** was confirmed by ^1H–^1H COSY analysis. Additionally, the relative stereochemistry was established on the basis of NOESY correlations as described in Figure 1. Conversion of **10**–**11**[7] was achieved by elimination of the tosylate moiety followed by hydrogenation of the resultant olefin. Krapcho reaction of **11** was performed using lithium chloride to afford hydrindane **12** as a 3:2 mixture of diastereoisomers with epimerization (Scheme 2).

At this stage, epimerization of the *trans*- and *cis*-hydrindanones **12** was performed under basic or acidic conditions as depicted in Table 1. Although no epimerization occurred when employing sodium ethoxide (entry 1) or aqueous hydrochloric acid (entry 2), reverse addition methods changed the ratio of **12**. Treatment of **12** with LDA and quenching with a tertiary alcohol as the proton source produced a 2:1 ratio of *cis*-hydrindanone **12a**[4h] and *trans*-isomer **12b**.[5] On the other hand, *cis*-hydrindanone **12b** doubled in ratio when TBMP (2,6-di-tertiary-butyl-4-methylphenol) was used as the proton source. Each stereoisomer was easily isolated by silica gel column chromatography, and *cis*-hydrindane **12a** was first used for the construction of (±)-*cis*-195A (**1**).

Elaboration of *cis*-hydrindane **12a** into (±)-*cis*-195A (**1**) was achieved by applying Oppolzer's procedure.[5] Specifically, **12a** was transformed into a 1:1 mixture of stereoisomers of oximes **3**, which were subjected to Beckmann rearrangement to afford lactam **2** as a single regioisomer in 67% overall yield. Lactam **2** was next converted into lactim-ether **13**, using trimethyloxoniumtetrafluoroborate in the presence of Hunig's base. Compound **13** was treated with propylmagnesium bromide under reflux in benzene followed by DIBAL-H at −78 °C to provide (±)-*cis*-195A (**1**) in 46% yield for three steps. In this sequence, benzene was found to be a

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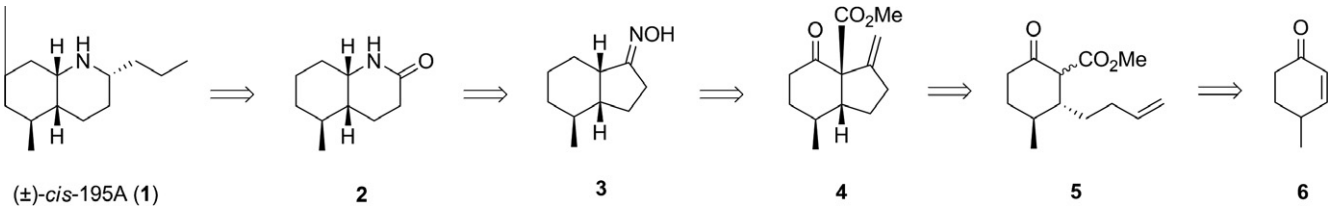
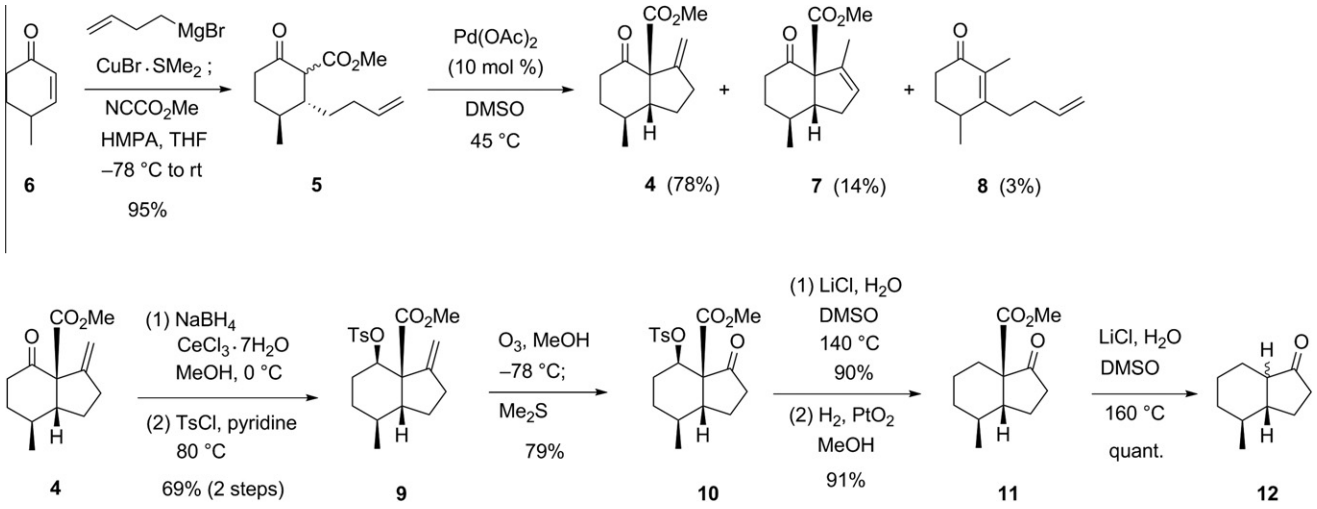


Scheme 1. Retrosynthetic analysis of *cis*-195A (**1**).



Scheme 2.

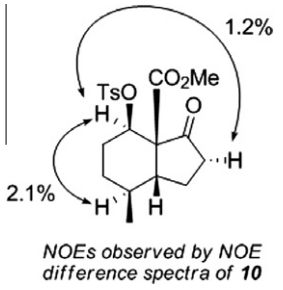


Figure 1.

crucial solvent for the Grignard reaction and the hydride ion attacked from the *cis* side with respect to the angular hydrogens in **14**. The NMR spectral data of synthetic (±)-**1** were identical to those previously reported.[5]

The preference for the hydride ion to add to intermediate **14** from the top can be explained by the Cieplak effect[8] through hyperconjugative stabilization of neighboring group electrons into the σ^*-orbital of the incipient carbon-nucleophile bond.

In contrast to *cis*-195A (**1**), little is known about the approaches to the synthesis of *trans*-195A (**16**), detected as a trace compound in dendrobatid frogs (Scheme 3).[9] Therefore, we pursued the total synthesis of *trans*-195A (**16**) from *trans*-hydrindane **12b**. Transformation of **12b** into lactam **15** through Beckmann rearrangement of the corresponding oximes of **12b** was accomplished in 55% yield. By analogy to the synthetic route used to access *cis*-195A (**1**), functional group manipulations of **15** gave rise to *trans*-195A (**16**)[9c] as shown in Scheme 4. As expected, hydride addition to intermediate **17** was highly stereoselective and occurred from the bottom. This stereoselectivity can be also rationalized by the Cieplak effect.[8]

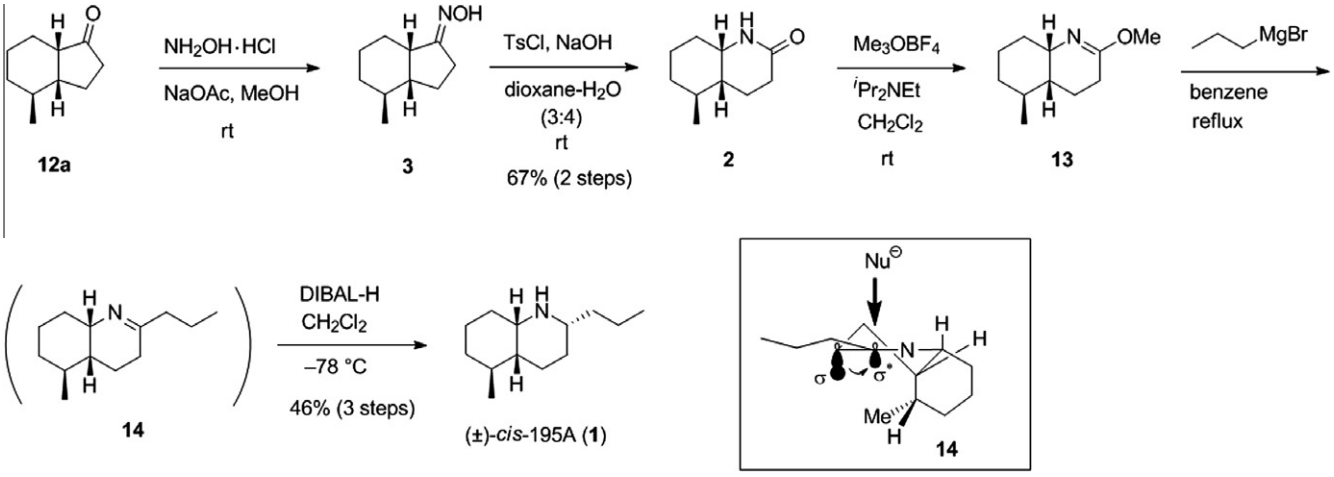
Table 1
Epimerization of hydrindanones **12a** and **12b**[a]

Entry	Conditions	Temperature (°C)	Ratio	
			12a	**12b**
1	NaOEt, EtOH	Reflux	3	2
2	10% HCl, EtOH	Reflux	3	2
3[b]	LDA, ^{t}BuOH	−78 °C	9	5
4[b]	LDA, TBMP	−78 °C	1	2

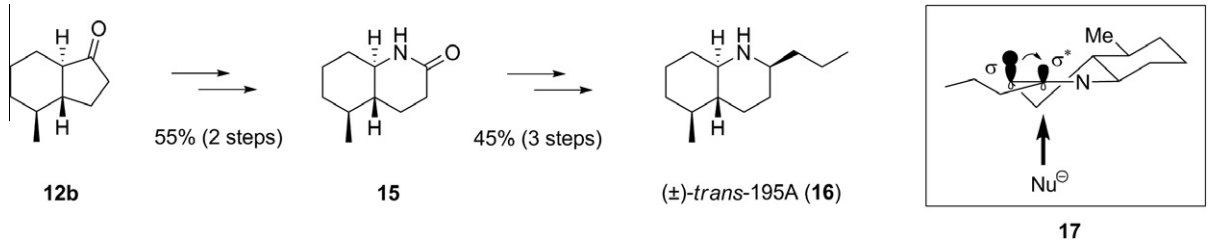
[a] After Krapcho reaction of keto ester **11**, a 3:2 mixture of *trans*- and *cis*-hydrindanones **12** was obtained.
[b] LDA wad added to a THF solution of **12** at −78 °C, and then alcohol was added at the same temperature.

An important advantage of the present strategy is that each diastereoisomer (**12a** and **12b**), isomeric only at the angular hydrogen, efficiently yields *cis*-195A (**1**) and *trans*-195A (**16**), respectively.

In conclusion, the decahydroquinoline alkaloids *cis*-195A (**1**) and *trans*-195A (**16**) were efficiently synthesized by using the same strategy. The synthetic approach included a palladium-catalyzed oxidative cyclization and a Beckmann rearrangement as key steps.



Scheme 3.



Scheme 4.

References and notes

1. Hibi, A.; Toyota, M. *Tetrahedron Lett.* **2009**, *50*, 4888–4891.
2. Original paper: Toyota, M.; Wada, T.; Fukumoto, K.; Ihara, M. *J. Am. Chem. Soc.* **1998**, *120*, 4916–4925; Review: Toyota, M.; Ihara, M. *Synlett* **2002**, 1211–1222; Applications: (a) Toyota, M.; Ilangovan, A.; Okamoto, R.; Masaki, M.; Arakawa, M.; Ihara, M. *Org. Lett.* **2002**, *4*, 4293–4296; (b) Toyota, M.; Rudyanto, M.; Ihara, M. *J. Org. Chem.* **2002**, *67*, 3374–3386; Aphidicolin synthesis: Toyota, M.; Sasaki, M.; Ihara, M. *Org. Lett.* **2003**, *8*, 1193–1195; Serofendic acids synthesis: Toyota, M.; Asano, T.; Ihara, M. *Org. Lett.* **2005**, *7*, 3929–3932.
3. Isolation: Daly, J. W.; Tokuyama, T.; Habermehl, G.; Karle, I. L.; Witkop, B. *Liebigs Ann. Chem.* **1969**, *729*, 198–204; Physiological property: Daly, J. W.; Nishizawa, Y.; Padgett, W. L.; Tokuyama, T.; McCloskey, P. J.; Waykole, L.; Schultz, A. G.; Aronstam, R. S. *Neurochem. Res.* **1991**, *16*, 1207–1212.
4. Recent total syntheses: (a) Padwa, A.; Heidelbaugh, T. M.; Kuethe, J. T. *J. Org. Chem.* **2000**, *65*, 2368–2378; (b) Oppolzer, W.; Flaskamp, E.; Bicher, L. *Helv. Chim. Acta* **2001**, *84*, 141–145; (c) Akashi, M.; Sato, Y.; Mori, M. *J. Org. Chem.* **2001**, *66*, 7873–7874; (d) Dijk, E. W.; Panella, L.; Pinho, P.; Naasz, R.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Tetrahedron* **2004**, *60*, 9687–9693; (e) Girard, N.; Hurvois, J.-P.; Moinet, C.; Toupet, L. *Eur. J. Org. Chem.* **2005**, 2269–2280; (f) Amat, M.; Griera, R.; Fabregat, R.; Molins, E.; Bosch, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 3348–3351; (g) Lauson, S.; Tremblay, F.; Gagnon, D.; Godbout, C.; Chabot, C.; Mercier-Shanks, C.; Perreault, S.; DeSeve, H.; Spino, C. *J. Org. Chem.* **2008**, *73*, 6239–6250; Our syntheses: (h) Toyota, M.; Asoh, T.; Matsuura, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 8687–8691; (i) Toyota, M.; Asoh, T.; Fukumoto, K. *Tetrahedron Lett.* **1996**, *37*, 4401–4404.
5. Oppolzer, W.; Fehr, C.; Warneke, J. *Helv. Chim. Acta* **1977**, *60*, 48–58.
6. Aubin, Y.; Audran, G.; Monti, H. *Tetrahedron Lett.* **2006**, *47*, 3669–3671.
7. *Data for new compounds*: compound **4**: IR (neat) 2953, 2929, 1740, 1705, 1651, 1238, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 (1H, dd, J = 2.0 and 2.0 Hz), 4.93 (1H, dd, J = 2.4 and 2.4 Hz), 3.73 (3H, s), 2.59–2.35 (5H, m), 1.93–1.87 (1H, m), 1.78–1.41 (4H, m), 1.04 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, C_6D_6) δ 206.1, 172.0, 149.1, 112.8, 72.8, 55.1, 52.8, 38.9, 33.4, 31.7, 30.2, 28.2, 20.2; LRMS m/z 222 (M^+), 190; HRMS calcd for $C_{13}H_{18}O_3$ (M^+) 222.1256, found 222.1252. Compound **9**: IR (neat) 1727, 1246, 1176, 911 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.86–7.73 (2H, m), 7.31–7.29 (2H, m), 5.27 (1H, dd, J = 8.4 and 5.2 Hz), 5.20 (1H, dd, J = 2.4 and 2.4 Hz), 5.01 (1H, dd, J = 2.4 and 2.4 Hz), 3.51 (3H, s), 2.43 (3H, s), 2.40–2.31 (1H, m), 2.09 (1H, ddd, J = 9.6, 6.0, and 4.0 Hz), 2.02–1.91 (2H, m), 1.75 (1H, ddd, J = 13.6, 9.2, and 4.4 Hz), 1.67–1.48 (3H, m), 1.34–1.23 (1H, m), 1.21–1.10 (1H, m), 0.88 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0, 147.8, 144.3, 134.6, 129.5, 129.5, 127.7, 127.7, 111.2, 84.4, 61.2, 52.4, 30.7, 30.3, 29.9, 27.4, 27.2, 26.4, 21.6, 19.8; LRMS m/z 378 (M^+), 346, 206, 147; HRMS calcd for $C_{20}H_{26}O_5S$ (M^+) 378.1501, found 378.1506. Compound **10**: mp 94.5–95.5 °C; IR (neat) 1756, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (2H, m), 7.32 (2H, m), 5.28 (1H, dd, J = 3.2 and 6.0 Hz), 3.64 (3H, s), 2.50 (1H, ddd, J = 6.8, 6.8, and 6.8 Hz), 2.44 (3H, s), 2.34 (1H, ddd, J = 17.2, 9.6, and 8.0 Hz), 2.18 (1H, ddd, J = 13.2, 8.0, and 5.0), 2.08–1.83 (5H, m), 1.59 (1H, m), 1.22 (1H, m), 0.95 (3H, d, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.2, 171.0, 144.8, 134.1, 129.8, 129.8, 127.9, 127.9, 80.4, 62.0, 53.0, 47.9, 37.2, 30.2, 25.5, 25.2, 24.8, 21.8, 19.9; LRMS m/z 208 [$(M-CH_3C_6H_4SO_3H)^+$]; HRMS calcd for $C_{19}H_{24}O_6S$ (M^+) 380.1294, $C_{12}H_{16}O_3$ [$(M-CH_3C_6H_4SO_3H)^+$] 208.1099, found 208.1099. Compound **11**: IR (neat) 1753, 1730, 1244, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (3H, s), 2.45–2.36 (1H, m), 2.29–2.20 (2H, m), 2.14–2.08 (1H, m), 1.94–1.89 (2H, m), 1.74–1.67 (1H, m), 1.65–1.57 (2H, m), 1.16–0.97 (3H, m), 0.99 (3H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.4, 173.0, 61.6, 52.7, 47.1, 34.9, 32.0, 31.8, 27.4, 22.8, 21.4, 20.7; LRMS m/z 210 (M^+); HRMS calcd for $C_{12}H_{18}O_3$ (M^+), 210.1256, found 210.1261.
8. Cieplak, A. S. *Chem. Rev.* **1999**, *99*, 1265–1336.
   Similar result was observed by Yamamoto and co-workers: Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831–2843. Additionally, stereoelectronic effects predict the stereochemical preferences in **14** and **17**, respectively. (a) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296. (b) Deslongchamps, P. *Stereoelectonic Effects in Organic Chemistry*; Pergamon Press: Oxford, 1983; pp 211–221.
9. (a) Garraffo, H. M.; Simon, L. D.; Daly, J. W.; Spande, T. F.; Jones, T. H. *Tetrahedron* **1994**, *50*. 1329–11338; (b) Spande, T. F.; Jain, P.; Garraffo, H. M.; Pannell, L. K.; Yeh, H. J. C.; Daly, J. W.; Fukumoto, S.; Tokuyama, T.; Torres; Snelling, R. R.; Jones, T. H. *J. Nat. Prod.* **1999**, *62*, 5–21; Total synthesis of (+)-*trans*-195A: (c) Holub, N.; Neidhöfer, J.; Blechert, S. *Org. Lett.* **2005**, *7*, 1227–1229.