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A Rhodium Carbene Cyclization–Cycloaddition Cascade Strategy toward the Pseudolaric Acids

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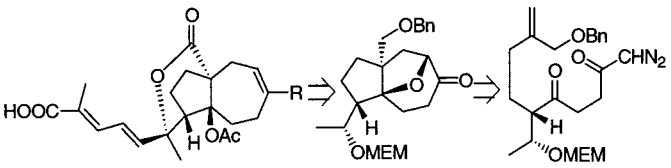
ABSTRACT

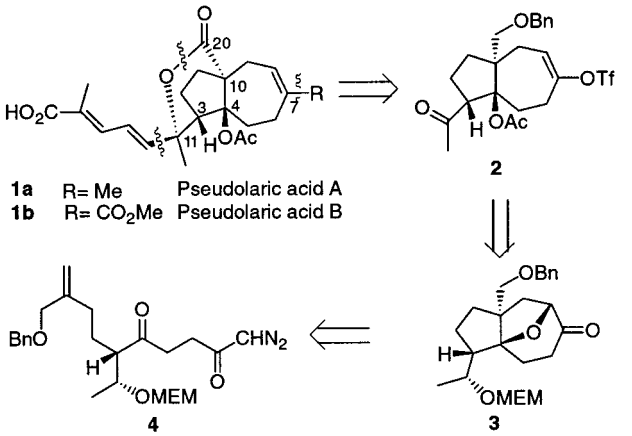


A rhodium carbene intramolecular cyclization–cycloaddition cascade was employed as the key reaction in the synthesis of the nucleus of the cytotoxic diterpenoids pseudolaric acids A and B.

The root bark of *Pseudolarix kaempferi* Gordon (Pinaceae), a tree native to China, has been a traditional medicinal herb called *tujinpi* for the treatment of dermatological fungal infections as early as the 17th century.[1] From this preparation, a family of diterpenoids called the pseudolaric acids have been isolated. Pseudolaric acid B (**1b**) has been determined to be the main antifungal component and has been evaluated to have antimicrobial activity comparable to that of amphotericin B against a number of fungal strains.[2] In vitro tests of pseudolaric acid A (**1a**) and pseudolaric acid B (**1b**) have demonstrated that they are cytotoxic to several cancer cell lines at sub-micromolar levels, while being relatively nontoxic in vivo.[1b,3] Characteristic of the pseudolaric acids is the unusual perhydroazulene skeleton bearing *trans*-fused acetoxy and lactone groups, which is an extremely rare arrangement for naturally occurring hydroazulenes. The installation of four contiguous stereocenters, of which three are quaternary, and the compactness of the molecule add to the synthetic challenge posed by this structure. Owing to their intriguing architecture and promising biological activities, a number of synthetic studies on the pseudolaric acids have appeared in the literature.[4−8]

Our strategy retroanalyzed the target molecules back to a common precursor, enol triflate **2**, from which both pseudolaric acids A and B, with methyl and carbomethoxy groups, respectively, at the C_7 position, can be derived via transition metal chemistry (Scheme 1).[9] This retrosynthetic analysis permits flexibility of substitution at C_7, as well as at C_{11}, to

Scheme 1. Retrosynthetic Analysis of Pseudolaric Acid A and B



(1) (a) Zhou, B. N.; Ying, B. P.; Song, G. Q.; Chen, Z. X.; Han, J.; Yan, Y. F. *Planta Med*. **1983**, *47*, 35. (b) Hamburger, M. O.; Shieh, H. L.; Zhou, B. N.; Pezzuto, J. M.; Cordell, G. A. *Magn. Reson. Chem.* **1989**, *27*, 1025.
(2) Li, E.; Clark, A. M.; Hufford, C. D. *J. Nat. Prod.* **1995**, *58*, 57.
(3) Pan, D. J.; Li. Z. L.; Hu, C. Q.; Chen, K.; Chang, J. J.; Lee, K. H. *Planta Med.* **1990**, *56*, 383.

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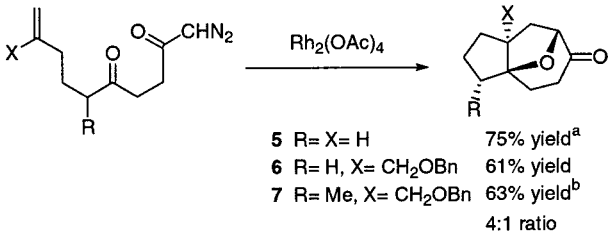
append different substituents for the synthesis of pseudolaric acid analogues. Enol triflate **2** can be obtained via a reductive elimination from the oxatricyclic ketone **3**, in which the tertiary acetate or alcohol has been masked as an oxygen bridge. This oxatricyclic ketone **3** was envisioned as the key intermediate that could be constructed by a reaction cascade initiated by the decomposition of an appropriately functionalized acyclic diazoketone **4**. The metal carbene would undergo cyclization intramolecularly with the carbonyl group to form a cyclic carbonyl ylide, followed by intramolecular [3 + 2] cycloaddition with the 2,2-disubstituted olefin to give the oxatricyclic intermediate.[10]

Previous studies in this area have established that the tandem metal carbene cyclization−cycloaddition sequence produces an adduct **5**, in which the bridgehead substituent (X = H) and the oxygen bridge are *trans* (Scheme 2).[11] Our

Scheme 2. Preliminary Studies on the Cyclization−Cycloaddition Cascade



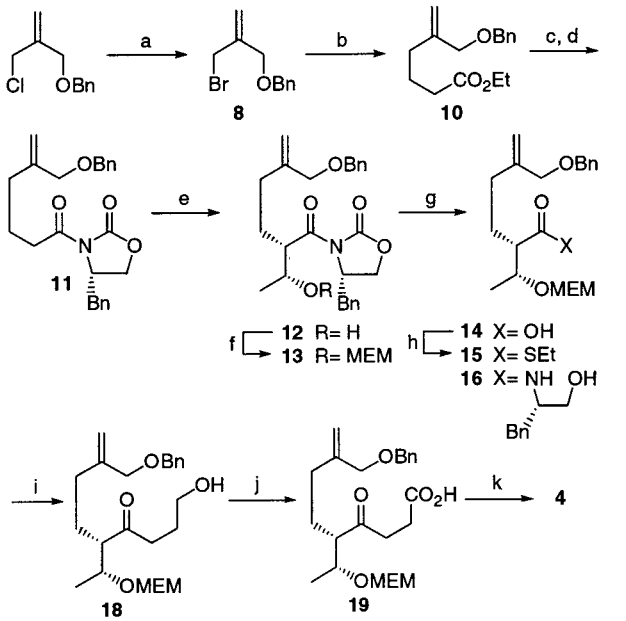
[a] Ref 11a. [b] Ref 13.

preliminary studies with a model substrate confirmed that the cyclization−cycloaddition cascade afforded cycloadduct **6**, in which a substituent (X = CH_2OBn) that can be oxidized to give the required carboxylate at C_{10} is also *trans* with respect to the oxygen bridge. Thus the *trans*-arrangement of the carboxylate at C_{10} and the acetoxy group at C_4 in the pseudolaric acid nucleus should be attainable via this cascade reaction.

However, it was not clear to what extent, if any, was the directing effect exerted by a substituent α to the carbonyl group of acyclic compound **4** on the diastereoselectivity of this reaction. We synthesized another model substrate that bears a methyl substituent α to the carbonyl group and found that the cyclization−cycloaddition sequence produced compound **7** as the major diastereomer with a selectivity of about 4:1. Gratifyingly, oxatricyclic product **7** has the substituent R= Me *cis* with respect to the bridgehead substituent (X = CH_2OBn), as required for the synthesis of the pseudolaric acids (Scheme 2).[12] With these preliminary results in hand, we proceeded to the enantioselective synthesis of the pseudolaric acids via a chiral synthesis of precursor **4**.

The optically pure cycloaddition precursor **4** was assembled as shown in Scheme 3. (2-Chloromethyl-allyloxymethyl)benzene[14] underwent halide exchange under phase transfer catalysis to afford bromide **8**. The zinc homoenolate **9** was then alkylated with allylic bromide **8** to give an 88%

Scheme 3 Synthesis of Precursor **4**[a]



[a] Reagents and Conditions: (a) LiBr, Aliquat 336, 60 °C, 2 h, 97%; (b) $IZnCH_2CH_2CO_2Et$ **9**, CuCN, THF, DMA, rt, 88%; (c) NaOH, MeOH, 98%; (d) *t*-BuCOCl, Et_3N, DMAP, (*S*)-4-benzyl-2-oxazolidone, THF, −78 °C to room temperature, 80%; (e) (i) *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C, (ii) CH_3CHO, −78 to 0 °C, 1 h, 67%, (92% based on recovered substrate); (f) MEMCl, DIPEA, CH_2Cl_2, rt, 93%; (g) (i) LiOH, H_2O_2, THF−H_2O, 0 °C, (ii) Na_2SO_3, 70%, **16** also obtained in 21% yield. (h) EtSH, DCC, DMAP, CH_2Cl_2, rt, 91%; (i) $ClMg(CH_2)_3OMgCl$ **17**, CuI, THF, 77%, (93% based on recovered substrate); (j) PDC, DMF, H_2O, 75%; (k)(i) *i*-BuOCOCl, Et_3N, THF, −20 °C, (ii) CH_2N_2, Et_2O, 0 °C to room temperature, 72%.

(4) Pan, B. C.; Chang, H. Y.; Cai, G. L.; Guo, Y. S. *Pure Appl. Chem.* **1989**, *61*, 389.
(5) Higuchi, R. I. Ph.D. Dissertation, Stanford University, Stanford, CA, 1995.
(6) Bonk, J. D. Ph.D. Dissertation, University of Mississippi, 1997.
(7) Chiu, P.; Chen, B.; Cheng, K. F. *Tetrahedron Lett.* **1998**, *39*, 9229.
(8) (a) Hu, Y.; Ou L.; Bai, D. *Tetrahedron Lett.* **1999**, *40*, 545. (b) Ou, L.; Hu, Y.; Song, G.; Bai, D. *Tetrahedron* **1999**, *55*, 13999.
(9) Review: Ritter, K. *Synthesis* **1993**, 737. Methylation of the vinyl triflate can be achieved using Me_2CuLi: McMurry, J. E.; Scott, W. J. *Tetrahedron Lett.* **1980**, *21*, 4313. Carbomethoxylation can be accomplished by Pd-catalyzed carbonylation: Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1985**, *26*, 1109.
(10) Reviews: (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; J. Wiley & Sons: New York, 1998; Chapter 7, pp 397−416.
(11) Leading references: (a) Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817. (b) McMills, M. C.; Zhuang L; Wright, D. L. Watt, W. *Tetrahedron Lett.* **1994**, *35*, 8311. (c) Dauben, W. G.; Dinges, J.; Smith, T. C. *J. Org. Chem.* **1993**, *58*, 7635.
(12) However, there is also a case in which the cyclization−cycloaddition of an α-substituted isomünchnone diazo precursor generated exclusively a product with opposite diastereoselectivity: Maier, M. E.; Evertz, K. *Tetrahedron Lett.* **1988**, *29*, 1677.
(13) The major isomer, **7**, can be clearly identified by a NOE between the methyl and the benzyloxymethylene protons: Ko, R. Y. Y., unpublished results.
(14) van der Louw, J.; van der Baan, L. L.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 6087.

yield of the homologated ester **10**. The alkylation of homoenolate **9** also proceeded with 2-chloromethyl-allyloxymethyl)benzene as the electrophile, albeit with a 50% yield.

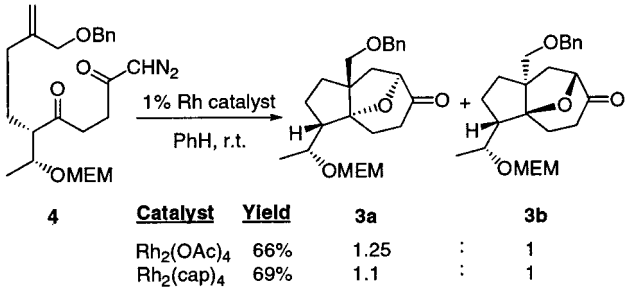
The absolute stereochemistry of the α substituent in **4** was installed by an enantioselective aldol reaction with acetaldehyde via Evan's auxiliary methodology.[15] Thus ester **10** was hydrolyzed and activated to couple with (*S*)-4-benzyl-2-oxazolidone. The acylated oxazolidinone **11** was converted to the boron enolate, which underwent the subsequent aldol condensation at −78 °C with acetaldehyde to provide aldol adduct **12** as one diastereomer in 67% yield, with recovered **11** in 27% yield.[16] The hydroxyl group of the aldol adduct was efficiently protected with the MEM group to give compound **13**.

The subsequent cleavage of the chiral auxiliary encountered some unanticipated hurdles. Our initial intention was to extend the carbonyl terminus of compound **13** by the addition of a three carbon nucleophile to its Weinreb amide derivative. Although conditions have been developed for the direct transamination of the acylated oxazolidone to the Weinreb amide via treatment with alkylaluminum amide reagents,[17] these methodologies failed with the hindered substrates **12** and **13**.[18] The products resulted predominantly from the attack of the amide at the oxazolidone carbonyl group. Fortunately, the hydrolysis of acylated oxazolidone **13** via lithium hydroperoxide was more successful and gave a 70% yield of acid **14**, although a 21% yield of alcohol **16** derived from oxazolidone carbonyl attack was still obtained.[19]

The plan to homologate acid **14** via its Weinreb amide was again thwarted by the inefficient conversion of **14** to the amide.[20] The chain extension was finally accomplished via thioester **15**, which could be prepared from acid **14** in excellent yield. The thioester proceeded to undergo chain extension via the cuprate derived from Grignard reagent **17**[21] to afford alcohol **18**.[22] Oxidation with PDC in the presence of water generated acid **19**. The preparation of the diazoketone **4** was accomplished by activation and treatment with diazomethane.

Treatment of the chiral precursor **4** with rhodium acetate induced the decomposition of the diazoketone and initiated the tandem intramolecular cyclization−cycloaddition cascade to give, in one step, the oxatricyclic product **3** in 66% yield as two diastereomers **3a** and **3b**, in a ratio of 1.25:1 (Scheme 4).

Scheme 4. Rhodium-Catalyzed Cyclization−Cycloaddition of **4**

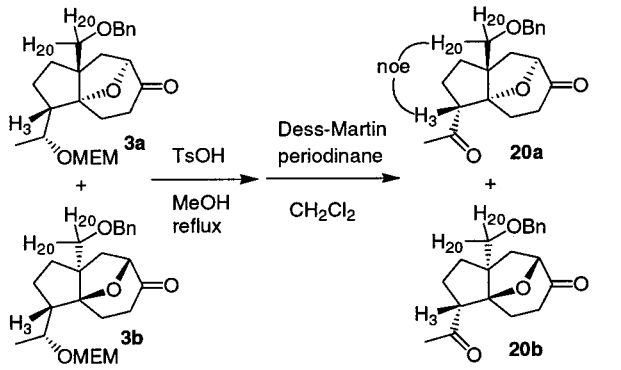


4	Catalyst	Yield	3a		3b
	$Rh_2(OAc)_4$	66%	1.25	:	1
	$Rh_2(cap)_4$	69%	1.1	:	1

In metal carbene reactions, the fact that the metal catalyst is still associated with the carbene after diazo decomposition is evidenced by the modulation of the chemoselectivity of carbene reactions using metal catalysts of varying strengths and by the ability of chiral catalysts to induce enantioselective carbene reactions.[23,24] Therefore, variations in the ligands of the rhodium catalyst could influence the stereochemical outcome of the cyclization−cycloaddition cascade. The use of another catalyst, $Rh_2(cap)_4$, was attempted in the intramolecular tandem cyclization−cycloaddition of diazoketone compound **4**. The reaction rate was noticeably slower than with rhodium acetate as a result of the ligands being less electron-deficient lactams. In the event, $Rh_2(cap)_4$ gave the cyclized product **3** in a comparable yield, with the ratio of diastereomers being slightly more in favor of the minor diastereomer **3b** than with $Rh_2(OAc)_4$.

The elucidation of the structures of the diastereomers was hampered by the difficulty in separating the two compounds of similar polarities. Furthermore, the ^1H NMR signals of the key protons H_3 and H_{20} overlapped with the peaks of other protons in the molecule (Scheme 5). Derivatization of **3a** and **3b** was done by deprotection of the MEM group followed by oxidation to produce diastereomeric diketones **20a** and **20b** respectively. When the 2-D NOESY spectra of these pure diketones were obtained, enhancement was

Scheme 5. Structure Elucidation of **3a** and **3b** via **20a** and **20b**



(15) (a) Cowden, C. J.; Paterson, I. *Org. React.* **1997**, *51*, 1. (b) Evans, D. A. *Aldrichimica Acta* **1982**, *15*, 23. (c) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.

(16) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 83.

(17) (a) Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc*. **1988**, *110*, 2506. (b) Evans, D. A.; Bender, S. L. *Tetrahedron Lett*. **1986**, *27*, 799. (c) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685.

(18) Reactions of substrates **9** or **10** with the aluminum amides derived from Me_3Al, Me_2AlCl, Et_2AlCl uniformly failed to produce the desired Weinreb amide.

(19) Compound **12** is presumably derived from the attack of the oxazolidone carbonyl by peroxide, reduction by sufite to the acyl carbamic acid, and decarboxylation.

(20) Using either DCC or BOP as coupling reagents, amide formation required 3−4 days and resulted in product yields of 44% and 36%, respectively.

(21) Normant, J. F.; Cahiez, G.; Alexakis, A. *Tetrahedron Lett.* **1978**, *33*, 3013.

(22) Anderson, R. J.; Henrick, C. A.; Rosenblum, L. D. *J. Am. Chem. Soc*. **1974**, *96*, 3654.

observed for protons H_3 and H_{20} in the spectrum of compound **20a** derived from the major isomer. On the other hand, the spectrum of pure **20b** showed the absence of an NOE cross-peak between the corresponding protons, thereby confirming the assignment of the structures of **3a** and **3b** to be as shown. Hence oxatricyclic compound **3b** is the intermediate to proceed with the synthesis.

It is not clear at this point why the desired diastereoselectivity deteriorated in the reaction of substrate **4**, compared with a similar precursor bearing a methyl substituent that was selective for the desired isomer **7**. The factors governing the observed diastereoselectivity in this cascade reaction will need to be further elucidated in order to improve the selectivity for the desired intermediate **3b**. Efforts will be directed toward completing the synthesis by the opening of the oxabicyclic core and the addition of a diene nucleophile to C_{11}. These results will be reported in due course.

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Supporting Information Available: Experimental procedures; ^{1}H NMR, ^{13}C NMR, IR, and MS spectral data for all products; and ^{1}H and ^{13}C NMR spectra of compounds **3b**, **4**, **6**−**8**, **10**−**16**, **18**−**19**, **20a**, and **20b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) (a) Padwa, A.; Austin, D. J.; Hornbuckle, S. R.; Semones, M. A.; Doyle, M. P.; Protopopova, M. N. *J. Am. Chem. Soc*. **1992**, *114*, 1874. (b) Padwa, A.; Austin, D, J.; Hornbuckle, S. F. *Tetrahedron Lett.* **1992**, *33*, 6427.

(24) (a) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc*. **1999**, *121*, 1417. (b) Hodgson, D. M.; Stupple, P. A.; Johnstone, C. *Chem. Commun*. **1999**, 2185.