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A Ring-Closing Metathesis-Based Approach to the Synthesis of (+)-Tetrabenazine

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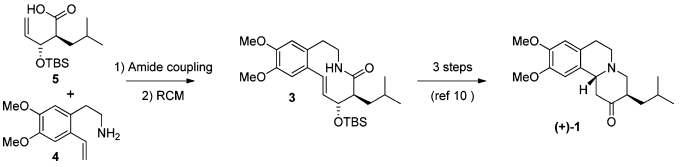
ABSTRACT



A modular stereoselective synthesis of the vesicular monoamine transport inhibitors (+)-tetrabenazine ((+)-1) and (+)-α-dihydrotetrabenazine ((+)-2) has been developed. The approach is based on amine 4 and acid 5 as the key building blocks, which were elaborated into macrolactam 3 by amide coupling and a subsequent highly *E*-selective RCM reaction. Macrolactam 3 could be converted into tetrabenazine in three known steps.

Tetrabenazine (TBZ, **1**; Figure 1) is a synthetic benzoquinolizine derivative and as such is structurally related to alkaloids of the protoberberine and the ipecac families.[1] TBZ was in clinical use for the treatment of neuroses and psychoses in several European countries in the early 1960s,[2] before it was withdrawn from the market in 1966.[3] Since 2008, racemic TBZ is the only drug approved by the US FDA for the treatment of chorea, one of the most common motor dysfunctions associated with Huntington's disease (HD);[3,4] it is also approved for the treatment of different movement disorders in a number of other countries.

TBZ reversibly binds to and inhibits the function of the vesicular monoamine transporter 2 (VMAT2),[5] which is responsible for monoamine transport from the cytoplasm into granular vesicles of presynaptic neurons. Inhibition of VMAT2 leads to enhanced cytoplasmic degradation of monoamine neurotransmitters by monoamine oxidases, and the resulting depletion of monoamines from nerve terminals is believed to underlie the beneficial effects of TBZ on hyperkinetic movement disorders, including Huntington's chorea.[3]

In vivo, TBZ undergoes rapid and extensive hepatic metabolism to the corresponding 2-hydroxy derivatives (dihydrotetrabenazines, Figure 1) as the pharmacologically active species.[3,4] Importantly, the binding of dihydrotetrabenazines to VMAT2 is highly stereospecific, with K_i values of 3.96 nM and 13.4 nM for the α- and β-dihydro derivatives **2**α and **2**β, respectively, which are derived from (+)-tetrabenazine ((+)-**1**);[6,7] in contrast, binding affinities for the corresponding reduction products derived from (−)-**1** are only in the micromolar range.[6,7] For TBZ itself, the literature data on stereospecific binding (or lack thereof) are contradictory.[6,8]

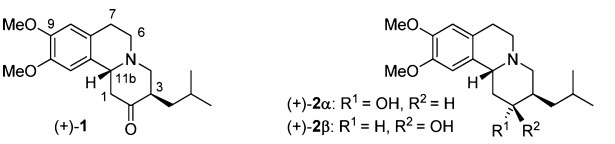


Figure 1. Structures of (+)-TBZ ((+)-**1**) and dihydro-TBZ (**2**).

(1) Brossi, A.; Lindlar, H.; Walter, M.; Schnider, O. *Helv. Chim. Acta* **1958**, *41*, 119. See also: Pletscher, A. *Science* **1957**, *126*, 507.
(2) Pletscher, A.; Brossi, A.; Gey, K. F. *Int. Rev. Neurobiol.* **1962**, *4*, 275.
(3) For a recent review on tetrabenazine, see: Guay, D. R. P. *Am. J. Geriatr. Pharmacother.* **2010**, *8*, 331.
(4) US Food and Drug Administration, Center for Drug Evaluation and Research. New Drug Application No. 21-894: Tetrabenazine. Medical and Clinical Pharmacology reviews.
(5) (a) Scherman, D.; Henry, J. P. *Biochem. Pharmacol.* **1980**, *29*, 1883.

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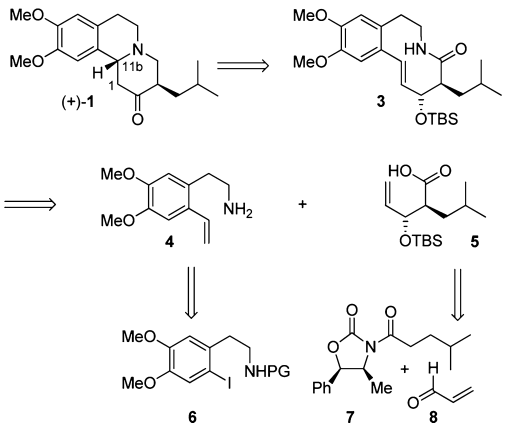
In light of the significant difference in VMAT2 inhibition between dihydrotetrabenazines derived from (+)- or (−)-**1**, stereoselective access to (+)-**1** is of considerable interest, also in the context of developing VMAT2-directed imaging agents.[9] So far, two asymmetric syntheses of (+)-**1** have been reported in the literature,[10,11] both of which depart from 6,7-dimethoxy-3,4-dihydroisoquinoline and deliver (+)-**1** in eight steps for the longest linear sequence (in both cases).[12]

Scheme 1. Retrosynthesis of (+)-Tetrabenazine ((+)-**1**)

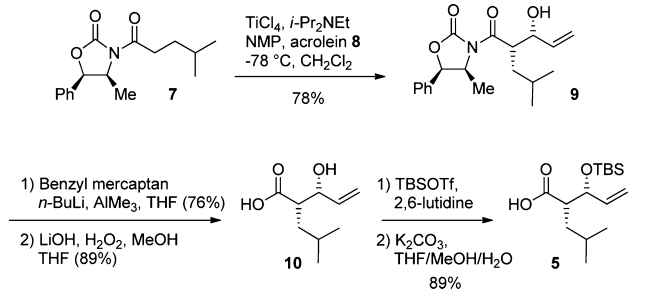


One of the objectives of our own work on tetrabenazine is the assessment of the VMAT-inhibitory activity of analogues with modifications in the central tetrahydropyridine ring, as no SAR information for this part of the tetrabenazine structure is available so far.[13] In this context, we have investigated an alternative, modular approach to (+)-**1** that would involve the separate installation of the stereocenter at C3 and that we felt could be adapted to the incorporation of substituents at the 6 and/or 7 position(s) or to changes in the size of the central ring more readily than the existing approaches.[14]

As illustrated in Scheme 1, the synthesis was to proceed through macrolactam **3**, whose acid-catalyzed cyclization to the quinolizine scaffold of (+)-**1** had been previously described by Suh and co-workers.[10] In contrast to this previous work, however, macrolactam **3** would not be the product of an intramolecular rearrangement but was envisaged to be formed through ring-closing olefin metathesis (RCM) between C1 and C11b (tetrabenazine numbering). The requisite diene would be obtained by amide bond formation between amine **4** and acid **5**; amine **4** would derive from an appropriately protected iodide **6** by way of Stille coupling with $Bu_3SnCH{=}CH_2$, while **5** was to be obtained via the stereoselective aldol reaction of the Evans oxazolidinone **7** and acrolein (**8**).

On the basis of previous literature reports,[15] initial attempts at carboxylic acid **5** involved reaction of the boron enolate of **7** with acrolein (**8**). However, while the desired aldol product was indeed formed under these conditions, the reaction proved to be poorly reproducible, with isolated yields ranging from 30 to 65%. As an alternative, the use of the Ti-enolate of **7** was investigated according to methodology that has been developed by Crimmins and co-workers.[16] Thus, treatment of **7** with $TiCl_4$ as a Lewis acid and 1 equiv of *N*-methyl-2-pyrrolidone as an additive at −78 °C followed by the addition of acrolein resulted in the formation of the desired 2*S*,3*R*-aldol product **9** in a reproducible fashion and in good yield (78%; Scheme 2). One other isomer was detectable by TLC, but this compound could be cleanly removed by flash chromatography (FC) and was not further characterized.

Scheme 2. Synthesis of Carboxylic Acid **5**



The anticipated and desired *R*-configuration at C3 of aldol product **9** was unequivocally established by Mosher ester analysis.[17,18] Reductive cleavage of the chiral

(6) Yao, Z.; Wei, X.; Wu, X.; Katz, J. L.; Kopajtic, T.; Greig, N. H.; Sun, H. *Eur. J. Med. Chem.* **2011**, *46*, 1841.

(7) See also: (a) Kilbourn, M. R.; Lee, L. C.; Heeg, M. J.; Jewett, D. M. *Chirality* **1997**, *9*, 59. (b) Kilbourn, M.; Lee, L.; Vander Borght, T.; Jewett, D.; Frey, K. *Eur. J. Pharmacol.* **1995**, *278*, 249.

(8) Yu, Q-s.; Luo, W.; Deschamps, J.; Holloway, H. W.; Kopajtic, T.; Katz, J. L.; Brossi, A.; Greig, N. H. *ACS Med. Chem. Lett* **2010**, *1*, 105.

(9) See, e.g.: (a) Malaisse, W. J.; Louchami, K.; Sener, A. *Nature Rev., Endocrin.* **2009**, *5*, 394. (b) Ravina, B.; Eidelberg, D.; Ahlskog, J. E.; Albin, R. L.; Brooks, D. J.; Carbon, M.; Dhawan, V.; Feigin, A.; Fahn, S.; Guttman, M.; Gwinn-Hardy, K.; McFarland, H.; Innis, R.; Katz, R. G.; Kieburtz, K.; Kish, S. J.; Lange, N.; Langston, J. W.; Marek, K.; Morin, L.; Moy, C.; Murphy, D.; Oertel, W. H.; Oliver, G.; Palesch, Y.; Powers, W.; Seibyl, J.; Sethi, K. D.; Shults, C. W.; Sheehy, P.; Stoessl, A. J.; Holloway, R. *Neurology* **2005**, *64*, 208.

(10) Paek, S.-M.; Kim, N.-J.; Shin, D.; Jung, J.-K.; Jung, J.-W.; Chang, D.-J.; Moon, H.; Suh, Y.-G. *Chem.—Eur. J.* **2010**, *16*, 4623.

(11) Rishel, M. J.; Amarasinghe, K. K. D.; Dinn, S. R.; Johnson, B. F. *J. Org. Chem.* **2009**, *74*, 4001.

(12) For a recent 10-step racemic synthesis of **1**, see: Son, Y. W.; Kwon, T. H.; Lee, J. K.; Pae, A. N.; Lee, J. Y.; Cho, Y. S.; Min, S.-J. *Org. Lett.* **2011**, *13*, 6500.

(13) For reviews on SAR studies on TBZ see: (a) Wimalasena, K. *Med. Res. Rev.* **2011**, *31*, 483. (b) Zheng, G.; Dwoskin, L. P.; Crooks, P. A. *AAPS J.* **2006**, *8*, E682.

(14) For both exisiting syntheses of (+)-**1** the stereocenter at C3 is installed in an intramolecular fashion (either by cyclization or rearrangement), with the corresponding precursor already incorporating a stereocenter at the position corresponding to C11b in **1**. It is well conceivable that the stereochemical outcome of these intramolecular steps would be affected by remote stereocenters at postions 6 and/or 7, but this would have to be established experimentally.

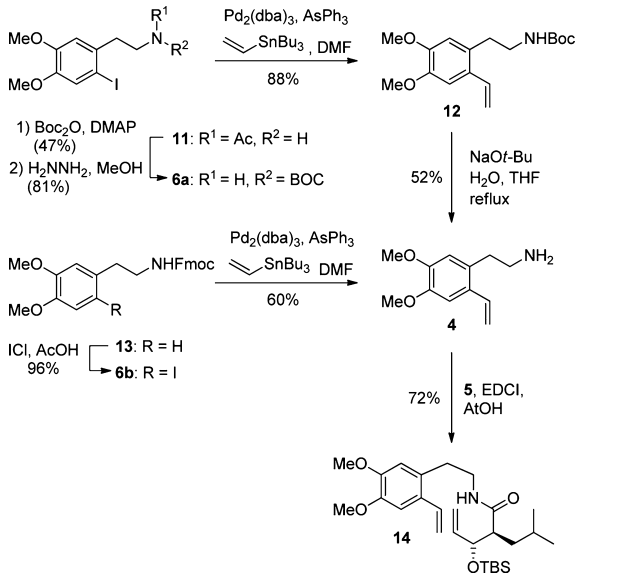
(15) Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999.

(16) Crimmins, M. T.; She, J. *Synlett* **2004**, *8*, 1371.

(17) (a) Hoye, T. R.; Jeffrey, C. S.; Shao, F. *Nature Protocols* **2007**, *2*, 2451. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

auxiliary in **9** with $LiBH_4$ gave a 1,3-diol that was converted into the corresponding acetonide by treatment with 2,2-dimethoxypropane and camphorsulfonic acid; *J* coupling constant analysis for this cyclic derivative confirmed the *syn* configuration of the C2 and C3 substituents in aldol product **9**.[18] TBS protection of the secondary hydroxyl group in **9** then turned out to be more challenging than expected. Thus, the reaction of **9** with TBSCl and imidazole proceeded very slowly and gave the desired TBS ether only in low yield (37%). Rather surprisingly, the yield obtained upon treatment of **9** with TBSOTf and 2,6-lutidine was even lower (9%); in addition, yields were not reproducible for either of these approaches. As a consequence, imide **9** was first converted into β-hydroxy acid **10** in a two-step sequence that involved cleavage of the auxiliary with benzyl mercaptan and *n*-BuLi (to form the corresponding thioester in 76% yield) followed by saponification of the thioester with LiOOH in MeOH/THF, which produced **10** in excellent yield (89%).[15] Reaction of **10** with 6 equiv of TBSOTf in the presence of 12 equiv of 2,6-lutidine gave a bis-silylated intermediate,[19] which upon treatment with K_2CO_3 in THF/MeOH/water (after aqueous workup of the silylation reaction) gave the desired building block **5** in 89% yield after FC (Scheme 2). It should be noted here that the attempted TBS protection of the intermittent thioester with TBSCl/imidazole was again unsuccessful, contrary to what has been reported in the literature.[15]

Scheme 3. Synthesis of Amine **4** and Diene **14**



For the synthesis of amine **4**, the two differently N-protected iodides **6a** and **6b** were explored as substrates for the crucial Stille coupling with $Bu_3SnCH{=}CH_2$ that serves to install one of the two terminal alkene moieties of the RCM precursor (Scheme 3).

The *N*-BOC derivative **6a** was prepared from known iodide **11**[20] by carbamoylation of the amide nitrogen with BOC_2O followed by selective cleavage of the acetamide moiety with hydrazine.[21] Stille coupling between **6a** and $Bu_3SnCH{=}CH_2$ in the presence of $Pd_2(dba)_3$ and Ph_3As then proceeded smoothly and provided the desired coupling product **12** in 88% yield. The efficiency of the coupling reaction was strongly dependent on the nature of the palladium ligand employed, with Ph_3As[22] leading to significantly enhanced yields over Ph_3P, which was used in initial experiments. Unfortunately, the only product obtained from **12** under standard acidic BOC cleavage conditions was 1,2,3,4-tetrahydro-6,7-dimethoxy-1-methylisoquinoline, while none of the desired amine **4** could be isolated. The transformation of **12** into **4** could eventually be accomplished by base-mediated removal of the BOC group,[23] albeit in very moderate yield of 52%.

In light of the low overall yield for the elaboration of iodide **11** into amine **4** we investigated the use of FMOC-protected amine **13** (obtained by reaction of β-(3,4-dimethoxyphenyl)ethylamine with Fmoc-OSu in 91% yield) as a possible alternative starting material for the preparation of **4**. Treatment of **13** with iodine chloride in glacial acetic acid gave iodide **6b** in excellent yield (96%); subsequent Stille coupling with $Bu_3SnCH{=}CH_2$ resulted in concomitant loss of the Fmoc group and provided amine **4** in 53% overall yield for the 4-step sequence from β-(3,4-dimethoxyphenyl)ethylamine, thus establishing efficient access to this building block.

The subsequent coupling of **4** with carboxylic acid **5** was accomplished with 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDCI) in the presence of 1-hydroxy-7-azabenzotriazole (AtOH) in DMF[24] and gave the desired diene **14** in good yield (72%).

While the strategy described above eventually provided satisfactory access to diene **14**, it had not been clear, initially, if the use of intermediate **6b** would in fact lead to an improved synthesis of amine **4**. Thus, we also investigated an alternative approach to **14**, where the critical Stille coupling would be performed only after amide bond formation. As illustrated in Scheme 4, this strategy was based on the EDCI/AtOH-mediated coupling of acid **5** with amine **16**, which provided amide **17** in high yield. The latter underwent Stille coupling with $Bu_3SnCH{=}CH_2$ ($Pd_2(dba)_3$, Ph_3As) in a highly efficient manner to furnish diene **14** in 88% yield.

The requisite amine **16** was prepared in two steps from nitrile **15**, which underwent regioselective iodination with iodine chloride in acetic acid (Scheme 4);[19] the resulting crystalline *o*-iodobenzylcyanide could then be reduced

(18) For NMR data, see the Supporting Information.

(19) Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544.

(20) Lete, E.; Collado, M. I.; Sotomayor, N.; Vicente, T.; Villa, M.-J. *J. Heterocycl. Chem.* **1995**, *32*, 1751.

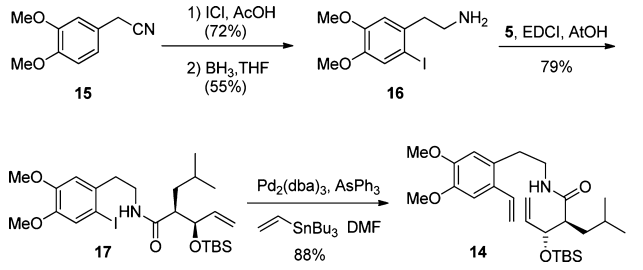
(21) The efficient direct iodination of *N*-BOC-β-(3,4-dimethoxyphenyl) ethylamine with $CF_3C(O)OAg/I_2$ has been described recently: Sawant, R. T.; Waghmode, S. B. *Synth. Commun.* **2011**, *41*, 2385.

(22) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.

(23) Tom, N. J.; Simon, W. M.; Frost, H. N.; Ewing, M. *Tetrahedron Lett.* **2004**, *45*, 905.

(24) Yang, D.; Zhang, Y.-H.; Li, B.; Zhang, D.-W. *J. Org. Chem.* **2004**, *69*, 7577.

Scheme 4. Alternative Synthesis of Diene 14



with borane in THF,[25] providing amine **16** in moderate, but still acceptable, yield (55%). Compared to the synthesis of diene **14** by the direct coupling of acid **5** and amine **4**, this alternative approach requires one additional step in the longest linear sequence (from **7**; seven vs six steps). This is reflected in a lower overall yield of 27% (from **7**) vs 30% for the route via amine **4**.

With diene **14** in hand, the stage was set for the exploration of the key metathesis reaction.[26] First attempts to accomplish RCM-based macrocyclization of **14** were carried out with the Grubbs II catalyst[27] in refluxing toluene. However, under these conditions none of the desired macrolactam was obtained; instead, dimer **18** (Scheme 5) was isolated in 41% yield together with traces of the stilbene that arises from cross metathesis of **14** with the benzylidene moiety of the catalyst.

No reaction was observed in dichloromethane or dichloroethane, with starting material being recovered unchanged, independent of the reaction temperature (rt or reflux). Gratifyingly, the use of the more reactive Hoveyda–Grubbs II catalyst[28] in refluxing toluene afforded the desired *E* configured macrolactam **3** in excellent yield, although the compound could only be isolated as a 10:1 mixture with dimer **18** (83%). The latter could not be chromatographically removed at this stage (Scheme 5).

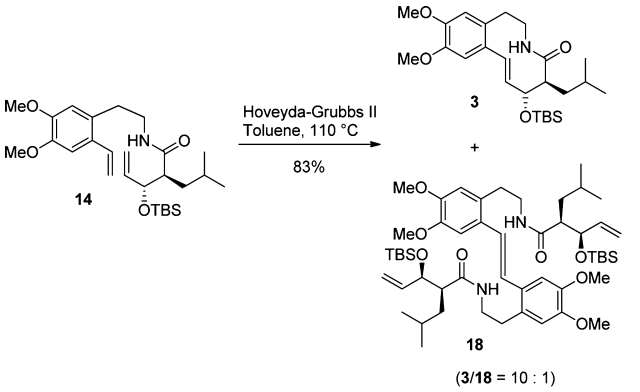
At the stage of macrolactam **3** our strategy toward (+)-**1** converged with the synthesis that had been previously developed by Suh and co-workers.[10] Thus, acid-induced ring closure of **3** with concomitant cleavage of the TBS ether gave 4-oxo benzoquinolizine **19** in 68% yield (based on the 10/1 mixture of **3** and **18**, Scheme 6); the deprotected form of dimer **18** from the RCM step could be readily removed at this stage. LAH reduction of **19** followed by TPAP oxidation then provided (+)-**1** in 29% overall yield from **3** (corrected for the purity of **3**; vs 42% reported by Suh).

(25) Fowler, J. S.; MacGregor, R. R.; Wolf, A. P. *J. Med. Chem.* **1976**, *19*, 356.

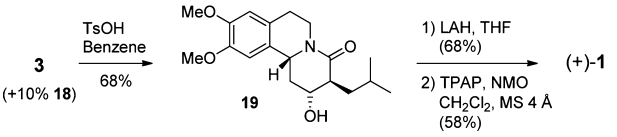
(26) For recent reviews on the metathesis reaction, see: (a) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490.

(27) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 2247.

Scheme 5. Ring-Closing Metathesis of **14**



Scheme 6. Final Steps in the Synthesis of (+)-Tetrabenazine[10]



In summary, we have established a new modular asymmetric route to (+)-tetrabenazine ((+)-**1**) that is based on the synthesis of key intermediate **3** by ring-closing metathesis. Lactam **3** was obtained in seven steps and 27% overall yield from acyl oxazolidinone **7** (i.e., with an average per step yield of 81%). Our approach to **3** is somewhat less efficient than the one elaborated by Suh and co-workers (four steps and 54% overall yield from 6,7-dimethoxy-3,4-dihydroisoquinoline); however, because of its modularity it should be more readily adaptable to the synthesis of tetrabenazine analogues with modifications of the central ring. Studies along these lines are currently ongoing in our laboratory.

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Supporting Information Available. Synthetic procedures, complete spectroscopic data, ^{1}H- and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

(28) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

The authors declare no competing financial interest.