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A concise asymmetric synthesis of (–)-rasfonin†

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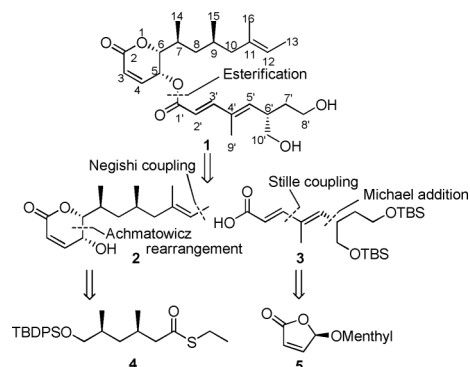
A very efficient total synthesis of the apoptosis inducer (–)-rasfonin has been developed using CuBr/JosiPhos catalyzed iterative asymmetric conjugate addition of MeMgBr and Feringa's butenolide.

Natural products containing α -pyranones (δ -lactones) show a variety of interesting biological properties.¹ As a prime example, rasfonin **1**, isolated from the fungus *Trichurus terrophilus*² and the fermented mycelium of *Taleromyces* species 3565-A1,³ has been reported as an active apoptosis inducer in *ras*-dependent cells.⁴ In connection with this finding, significant proliferation suppression of mouse splenic lymphocytes stimulated with mitogens, concanavalin A and lipopolysaccharide, was reported.⁴

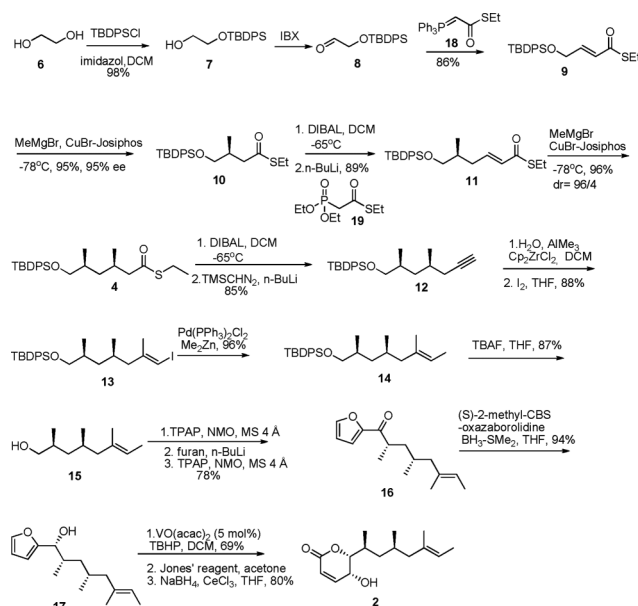
Due to the potential use of (–)-**1** in the development of cancer chemotherapeutics, a versatile synthetic route to rasfonin is required to establish which parts of the molecule are important for activity, and to pin down its target protein(s). The first total synthesis of (–)-**1**, reported by Ishibashi and co-workers in 2003, aimed at structure elucidation and absolute configuration determination.^{2,5} A second synthesis, reported by the group of Boeckman in 2006,⁶ was based on the use of camphor lactam chiral auxiliaries in order to allow the synthesis of different stereoisomers. As no follow-up appeared in chemical biology, we felt that a concise synthesis of **1**, taking advantage of highly efficient and selective catalytic methods and making this compound and analogs more readily available, could greatly stimulate biological studies. Herein, we report the asymmetric synthesis of (–)-**1** in a highly efficient and selective manner.

In our retrosynthetic analysis (Scheme 1), (–)-rasfonin **1** was disconnected into upper half **2** and lower half **3**. The former was planned to be obtained from **4**, in turn prepared *via* our iterative catalytic asymmetric conjugate addition protocol to deoxypropionates,⁷ in combination with a stereospecific Achmatowicz rearrangement.⁷ The lower part, **3**, should in principle be accessible starting from readily available enantiopure Feringa's menthyl butenolide **5**.⁸

Syn-1,3-dimethyl thioester **4** was synthesized in an excellent 57% overall yield starting from ethylene glycol **6** by CuBr/JosiPhos catalyzed iterative asymmetric conjugate addition of MeMgBr

Scheme 1 Retrosynthesis of (–)-rasfonin **1**.

(Scheme 2).⁹ Mono-protection of ethylene glycol **6** gave alcohol **7**. IBX oxidation of alcohol **7** followed by Wittig reaction using Wittig reagent **18** afforded substrate **9** in 86% yield. Substrate **9** gave excellent yield and enantioselectivity (95%, 95% ee) of compound **10** using CuBr/JosiPhos catalyzed conjugate addition of MeMgBr. DIBAL reduction of compound **10** followed by HWE olefination using reagent **19** gave thioester **11** in 89% yield. The excellent *syn* selectivity (96 : 4) of the second asymmetric conjugate addition of MeMgBr catalyzed by CuBr/JosiPhos gave dimethyl

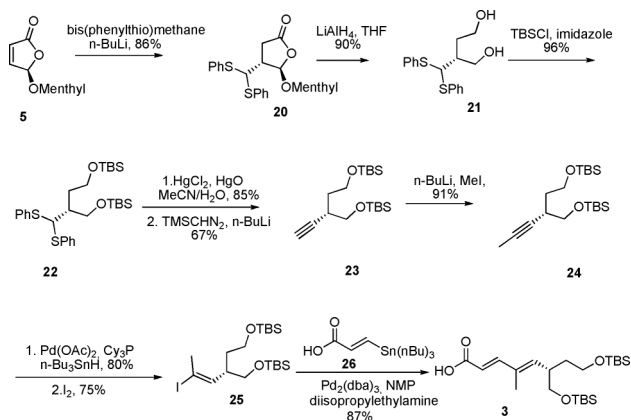
Scheme 2 Synthesis of upper half of (–)-rasfonin **1**.

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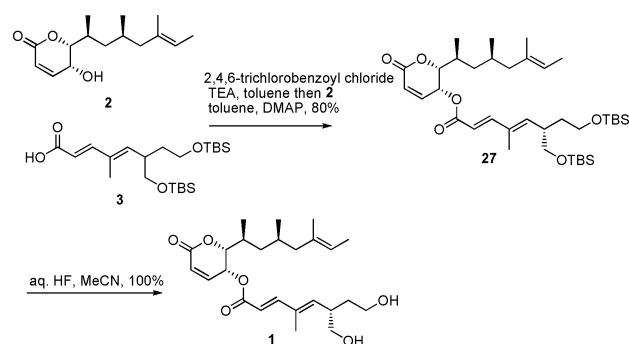
thioester **4** in 96% yield. Reduction of **4** with DIBAL afforded the corresponding aldehyde which was used immediately to form the terminal alkyne **12** by addition of lithiated trimethylsilyldiazomethane involving a Colvin rearrangement.¹⁰ Vinyl iodide **13** was subsequently prepared by Zr-catalyzed methylalumination,¹¹ followed by Negishi cross coupling¹² with ZnMe_2 to afford alkene **14**, which after deprotection with TBAF provided alcohol **15** in 87% yield. Ley oxidation¹³ of **15** afforded the corresponding aldehyde which was treated with 2-furyl lithium to give the corresponding furyl alcohol in 88% yield (*syn:anti* = 2:1). Subsequent Ley oxidation of this mixture gave ketone **16** in 98% yield which was in turn treated with (*S*)-CBS reagent and borane¹⁴ to afford furyl alcohol **17** in an excellent 94% yield and a *syn:anti* ratio >98:2. Stereospecific Achmatowicz rearrangement¹⁵ of **17** with vanadyl acetylacetonate and *tert*-butylhydroperoxide afforded the hemi-acetal in 69% yield which was subsequently oxidized by Jones' reagent¹⁶ to the corresponding ketolactone. Finally, Luche reduction¹⁷ gave the upper half **2** as the only diastereomer.

The stereogenic center in the lower half of (–)-rasfonin was introduced by Michael addition of lithium bis(phenylthio)methane⁸ to butenolide **5** to provide *trans*-**20** as the single diastereomer in 86% yield (Scheme 3). Full reduction of **20** by LiAlH_4 afforded diol **21** in 90% yield which after protection provided **22** in 96% yield. Unmasking of dithiane **22** by HgCl_2 and HgO in a mixture of acetonitrile and water¹⁸ went smoothly and afforded the free aldehyde in 85% yield which upon treatment with lithiated trimethylsilyldiazomethane provided the terminal alkyne **23** in 67% yield. Terminal alkylation of the alkyne moiety to give **24** was performed by lithiation followed by quenching with methyl iodide. The subsequent Pd-catalyzed hydrostannation of alkyne **24** with catalytic $\text{Pd}(\text{PPh}_3)\text{Cl}_2$ initially gave low yield and incomplete conversion. We encountered this problem before,¹⁹ and again the method proposed by Semmelhack and Hooley²⁰ strongly improved the outcome. Switching to catalytic $\text{Pd}(\text{OAc})_2$ and tricyclohexyl phosphine, with hexane as the solvent, led to complete conversion and 80% yield in 20 min! Vinyl iodide **25** was subsequently obtained in 75% yield by treating this stannylated compound with iodine. Stille coupling of acid **26**²¹ and **25** provided lower half **3** in 87% yield.



Scheme 3 Synthesis of the lower half of (–)-rasfonin **1**.

The coupling of the upper half **2** and lower half **3** of (–)-rasfonin was achieved by Yamaguchi esterification²² in 80% yield (Scheme 4). Desilylation initially was not satisfactory as treatment with



Scheme 4 Coupling of the upper half and lower half to give (–)-rasfonin **1**.

camphorsulfonic acid gave only 40% yield.⁶ Fortunately, switching to aq. HF in acetonitrile²³ gave in a close to quantitative yield (–)-rasfonin whose optical rotation and spectroscopic data agreed with the reported values (except for the presence of approx. 5% of a diastereomer that could not be separated).

In conclusion, a very efficient total synthesis of the apoptosis inducer (–)-rasfonin has been developed. $\text{CuBr}/\text{Josiphos}$ catalyzed iterative asymmetric conjugate addition of MeMgBr has been employed to install the stereogenic centers in the upper half side chain with excellent yield and stereoselectivity. The hydroxylactone core could be prepared by a subsequent stereospecific hydroxy-directed Achmatowicz rearrangement followed by an oxidation–reduction sequence. The synthesis of the lower half **3** makes use of the perfect transfer of chirality in the conjugate addition to butenolide **5** followed by selective construction of the *E,E*-diene-ester part. The availability of an effective route to rasfonin now allows us to study its role in inhibiting the Ras signalling pathway, provides access to functional analogs and might lead to the identification of its target protein.

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Notes and references

- (a) V. Shekhar, D. K. Reddy, V. Suresh, D. C. Babu and Y. Venkateswarlu, *Tetrahedron Lett.*, 2010, **51**, 946; (b) A. Favre, F. Carreaux, M. Deligny and B. Carboni, *Eur. J. Org. Chem.*, 2008, 4900; (c) L. Dong, V. A. Gordon, R. L. Grange, J. Johns, P. G. Parsons, A. Porzelle, P. Reddell, H. Schill and C. M. Williams, *J. Am. Chem. Soc.*, 2008, **130**, 15262.
- K. Akiyama, S. Kawamoto, H. Fujimoto and M. Ishibashi, *Tetrahedron Lett.*, 2003, **44**, 8427.
- T. Tomikawa, K. Shin-Ya, K. Furihato, T. Kinoshita, A. Miyajima, H. Seto and Y. Hayakawa, *J. Antibiot.*, 2000, **53**, 848.
- (a) H. Fujimoto, E. Sone, E. Okuyama, M. Ishibashi, 120th Annual Meeting of the Pharmaceutical Society of Japan, Abstracts of Papers 2, 2000; p 68; (b) O. Rocks, A. Peyker, M. Kahms, P. J. Vermeer, C. Koerner, M. Lumbierres, J. Kuhlmann, H. Waldmann, A. Wittinghofer and P. I. H. Bastiaens, *Science*, 2005, **307**, 1746; (c) L. Brunsveld, J. Kuhlmann, K. Alexandrov, A. Wittinghofer, R. S. Goody and H. Waldmann, *Angew. Chem., Int. Ed.*, 2006, **45**, 6622; (d) F. J. Dekker, O. Rocks, N. Vartak, S. Menninger, C. Hedberg, R. Balamurugan, S. Wetzel, S. Renner, M. Gerauer, B. Scholermann, M. Rusch, J. W.

- Kramer, D. Rauh, G. W. Coates, L. Brunsveld, P. I. H. Bastiaens and H. Waldmann, *Nat. Chem. Biol.*, 2010, **6**, 449.
- 5 K. Akiyama, S. Yamamoto, H. Fujimoto and M. Ishibashi, *Tetrahedron*, 2005, **61**, 1827.
- 6 R. K. Boeckman Jr., J. E. Pero and D. J. Boehmler, *J. Am. Chem. Soc.*, 2006, **128**, 11032.
- 7 (a) R. D. Mazery, M. Pullez, F. López, S. R. Harutyunyan, A. J. Minnaard and B. L. Feringa, *J. Am. Chem. Soc.*, 2005, **127**, 9966; (b) B. ter Horst, B. L. Feringa and A. J. Minnaard, *Chem. Commun.*, 2010, **46**, 2535.
- 8 (a) B. L. Feringa, B. D. Lange and J. C. de Jong, *J. Org. Chem.*, 1989, **54**, 2471; (b) A. van Oeveren and B. L. Feringa, *J. Org. Chem.*, 1996, **61**, 2920; (c) A. van Oeveren, J. F. G. A. Jansen and B. L. Feringa, *J. Org. Chem.*, 1994, **59**, 5999.
- 9 B. ter Horst, B. L. Feringa and A. J. Minnaard, *Org. Lett.*, 2007, **9**, 3013.
- 10 B. M. Trost, J. Waser and A. Meyer, *J. Am. Chem. Soc.*, 2007, **129**, 14556.
- 11 G. Zhu and E. Negishi, *Chem.–Eur. J.*, 2008, **14**, 311.
- 12 O. Robles and F. E. McDonald, *Org. Lett.*, 2009, **11**, 5498.
- 13 G. E. Keck, C. E. Knutson and S. A. Wiles, *Org. Lett.*, 2001, **3**, 707.
- 14 S. F. Sabes, R. A. Urbaneck and C. J. Forsyth, *J. Am. Chem. Soc.*, 1998, **120**, 2534.
- 15 J. A. Henderson, K. L. Jackson and A. J. Phillips, *Org. Lett.*, 2007, **9**, 5299.
- 16 A. Furstner and T. Nagano, *J. Am. Chem. Soc.*, 2007, **129**, 1906.
- 17 J. M. Harris and G. A. O'Doherty, *Org. Lett.*, 2000, **2**, 2983.
- 18 S. C. Sinha and E. Keinan, *J. Org. Chem.*, 1997, **62**, 377.
- 19 R. P. van Summeren, B. L. Feringa and A. J. Minnaard, *Org. Biomol. Chem.*, 2005, **3**, 2524.
- 20 M. F. Semmelhack and R. J. Hooley, *Tetrahedron Lett.*, 2003, **44**, 5737.
- 21 J. Thibonnet, V. Launay, M. Abarbri, A. Duchene and J. Parrain, *Tetrahedron Lett.*, 1998, **39**, 4277.
- 22 K. Ghosh, Y. Wang and J. T. Kim, *J. Org. Chem.*, 2001, **66**, 8973.
- 23 R. F. Newton and D. P. Reynolds, *Tetrahedron Lett.*, 1979, **20**, 3981.