

(51) International Patent Classification:
C07D 493/22 (2006.01)(21) International Application Number:
PCT/US2018/041005(22) International Filing Date:
06 July 2018 (06.07.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/529,333 06 July 2017 (06.07.2017) US
62/529,310 06 July 2017 (06.07.2017) US

(71) Applicants: PRESIDENT AND FELLOWS OF HARVARD COLLEGE [US/US]; 17 Quincy Street, Cambridge, MA 02138 (US). EISAI R & D MANAGEMENT CO., LTD. [JP/JP]; 4-6-10 Koishikawa, Bunkyo-ku, Tokyo, 112-8088 (JP).

(72) Inventor; and

(71) Applicant: FUKUYAMA, Takashi [JP/JP]; Eisai Co., Ltd., Tsukuba Research Laboratories, 5-1-3 Tokodai, Tsukuba-shi, Ibaraki, 300-2635 (JP).

(72) Inventors: KISHI, Yoshito; 75 Cambridge Parkway, Unit E902, Cambridge, MA 02142-1233 (US). AI, Yanran; 115 Christina Landing Dr. #508, Wilmington, DE 19801 (US). YE, Ning; Room 2807, Block 4, Central Park, #66, Jinhua Road, Suzhou Industrial Park, Suzhou, 215028 (CN). WANG, Qiaoyi; 1503 Stearns Hill Road, Waltham, MA 02451 (US). YAHATA, Kenzo; #102 D14, 2-7 Momoyamadaai Suita, Osaka 565-0854 (JP). ISO, Kentaro; 3-46-11 Rafina 204 Gakuenomori, Tsukuba Ibaraki 305-0816 (JP). NAINI, Santhosh Reddy; 16 Old Colony Lane, Apart-

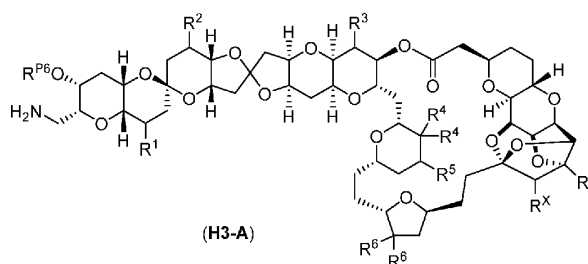
ment 5, Arlington, MA 02476 (US). YAMASHITA, Shuji; 434-5-202 Ichigao-cho, Aoba-ku, Yokohama 225-0024 (JP). LEE, Jihoon; 105-701, 12 Gyeongsu-daero, 1394 Beon-gil, Manan-gu 13907 (KR). OHASHI, Isao; c/o Eisai Co., Ltd., Tsukuba Research Laboratories, 5-1-3 Tokodai, Tsukuba-shi, Ibaraki 300-2635 (JP).

(74) Agent: HAMZIK, Philip J.; Wolf, Greenfield & Sacks, P.C., 600 Atlantic Avenue, Boston, MA 02210-2206 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

(54) Title: SYNTHESIS OF HALICHONDRIINS



(57) Abstract: The present invention provides methods for the synthesis of ketones involving a Ni/Zr-mediated coupling reaction. The Ni/Zr-mediated ketolization reactions can be used in the synthesis of halichondrins (e.g., halichondrin A, B, C; homohalichondrin A, B, C; norhalichondrin A, B, C), and analogs thereof. Therefore, the present invention also provides synthetic methods useful for the synthesis of halichondrins, and analogs thereof. Also provided herein are compounds (i.e., intermediates) useful in the synthesis of halichondrins, and analogs thereof. In particular, the present invention provides methods and compounds useful in the synthesis of compound of Formula (H3-A)

[Continued on next page]

Published:

- with international search report (Art. 21(3))
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))