

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau

(43) International Publication Date
16 September 2021 (16.09.2021)



(10) International Publication Number
WO 2021/183542 A1

(51) International Patent Classification:

C07K 5/02 (2006.01) C07C 211/63 (2006.01)
C07K 5/062 (2006.01) C07C 271/22 (2006.01)
C07C 211/35 (2006.01) C07D 207/08 (2006.01)

(21) International Application Number:

PCT/US2021/021547

(22) International Filing Date:

09 March 2021 (09.03.2021)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

62/987,150 09 March 2020 (09.03.2020) US

(71) Applicant: **SIGMA-ALDRICH CO., LLC** [US/US];
3050 Spruce Street, St. Louis, MO 63103 (US).

(72) Inventors: **GOEDDEL, David**; c/o Sigma-Aldrich Co.,
LLC, 3050 Spruce Street, St. Louis, MO 63103 (US).
WALKER, James; c/o Sigma-Aldrich Co., LLC, 3050
Spruce Street, St. Louis, MO 63103 (US). **GROSO, Emilia**;
c/o Sigma-Aldrich Co., LLC, 3050 Spruce Street, St. Louis,
MO 63103 (US). **BEMOWSKI, Ross**; c/o Sigma-Aldrich
Co., LLC, 3050 Spruce Street, St. Louis, MO 63103 (US).
BERG, Logan; c/o Sigma-Aldrich Co., LLC, 3050 Spruce
Street, St. Louis, MO 63103 (US).

(74) Agent: **FROST, Kristin, J.** et al.; Sigma-Aldrich Co.
LLC, c/o EMD Millipore Corporation, 400 Summit Drive,
Burlington, MA 01803 (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, IT, 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, ST, SV, SY, TH, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, 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: EFFICIENT PREPARATION OF DOLASTATIN AND AURISTATIN ANALOGS THROUGH A COMMON INTER-MEDIATE

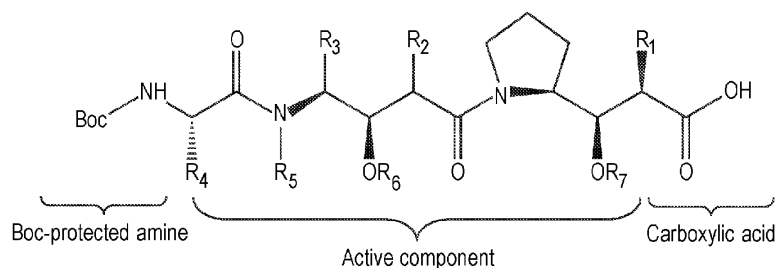


FIG. 1

(57) Abstract: Methods for making a dolastatin, auristatin or related compounds comprising the steps of providing a universal dolastatin core of Formula (I) reacting the C-terminal carboxylic acid group with an amine (A) to form an amide bond and reacting the N-terminal amine with a carboxylic acid (CA) to form an amide bond, wherein the steps can be performed in either order. Also provided are an isolated salt of the universal dolastatin core for use in preparation of dolastatins, auristatins and related compounds. Also provided are a number of intermediates and process steps which are useful for the preparation of high purity dolastatin core and high purity dolastatin and auristatin compounds.

[Continued on next page]



WO 2021/183542 A1

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))*