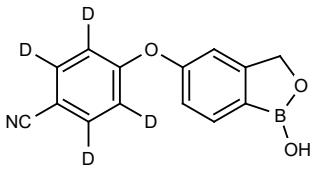
BDG SYNTHESIS

Certificate of Analysis

BDG Synthesis certifies that this reference material meets or exceeds the specifications stated herein.

Neil Beare, PhD, Director
27 August 2018

Name:	**Crisaborole-d_4**
CAS Number:	906673-24-3 (unlabelled)
Structure:	
Molecular Weight:	$C_{14}H_6D_4BNO_3$ = 255.07
Lot Number:	BDG 15957.6
Appearance:	White, crystalline solid
Corrected Purity:	99.8 % (HPLC) - 0.7 % (water) = 99.1 %
Isotopic Purity:	Under 0.5 % d_0
Re-test Date:	27 August 2023

Storage and Handling:

Temperature:	refrigerate for prolonged storage; may be handled and shipped at ambient temperature.
Humidity:	not believed to be hygroscopic; may be handled in normal laboratory atmosphere.
Light:	protect from strong sunlight.
Caution:	only experienced laboratory personnel should handle the material.

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Identity and Purity

Proton NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration are greatly diminished, compared with the spectrum of unlabelled material, indicating clean deuteration.
Residual Solvents: a trace (under 0.1 % *w/w*) of methanol is observed.
Impurities: no significant impurities are evident in the spectrum.

Carbon-13 NMR Spectrum

Identity: the signals are consistent with the proposed structure and in accord with literature where available.
Isotopic Labelling: signals at the sites of deuteration have collapsed to small multiplets compared with the spectrum of unlabelled material, indicating clean deuteration.

High-resolution Mass Spectrum (ESI-)

Found *m/z* 254.0937. $C_{14}H_5D_4BNO_3$ $[M-H]^-$ requires *m/z* 254.0935. The deviation of 0.9 ppm is within normally accepted limits for the establishment of identity by HRMS. No signal for d_0 material was seen (detection limit about 0.5 %).

HPLC

A sharp, slightly tailing peak is observed (99.8 %). Note: in the absence of reference materials for preparing calibration curves, it is assumed that all peaks have the same detector response. Where possible, the conditions of analysis follow a pharmacopeial or literature method, or have been adapted from same.

Elemental Analysis

	Found:	C 65.29, H 2.34, D 3.03, N 5.36 %
$C_{14}H_6D_4BNO_3 \cdot 0.1H_2O$	Requires:	C 65.46, H 2.43, D 3.14, N 5.45 %, H_2O 0.70 %
$C_{14}H_6D_4BNO_3$	Requires:	C 65.92, H 2.37, D 3.16, N 5.49 %

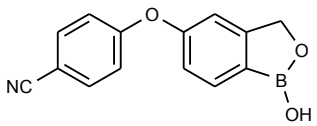
The elemental analyses fall slightly outside those expected for anhydrous material; the presence of water is reasonably expected from the method of purification and/or the type of material, and the "best-fit" hydrated molecular formula is given. In the absence of a Karl-Fischer water analysis, we recommend that the "best-fit" water content be used when determining corrected purity.

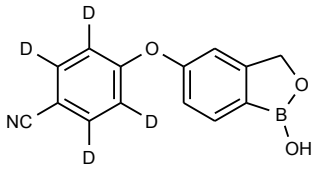
The available quantity of custom-synthesised material is always small, and this limits the extent and type of analytical data which can be obtained. This Certificate is presented in descriptive format for use by analytical chemists who are trained in the use of custom-synthesised materials. Custom materials often contain higher levels of residual solvents and/or water, and we urge you to use the corrected purity where needed rather than the raw HPLC purity. This compound is intended for use as an analytical reference material and it is not for human administration. Structures are shown with relative stereochemistry unless otherwise specified.

The re-test date is assigned from experience gained with the material in the laboratory and/or on storage. It is not possible to perform formal storage studies because of the small amount of material available.

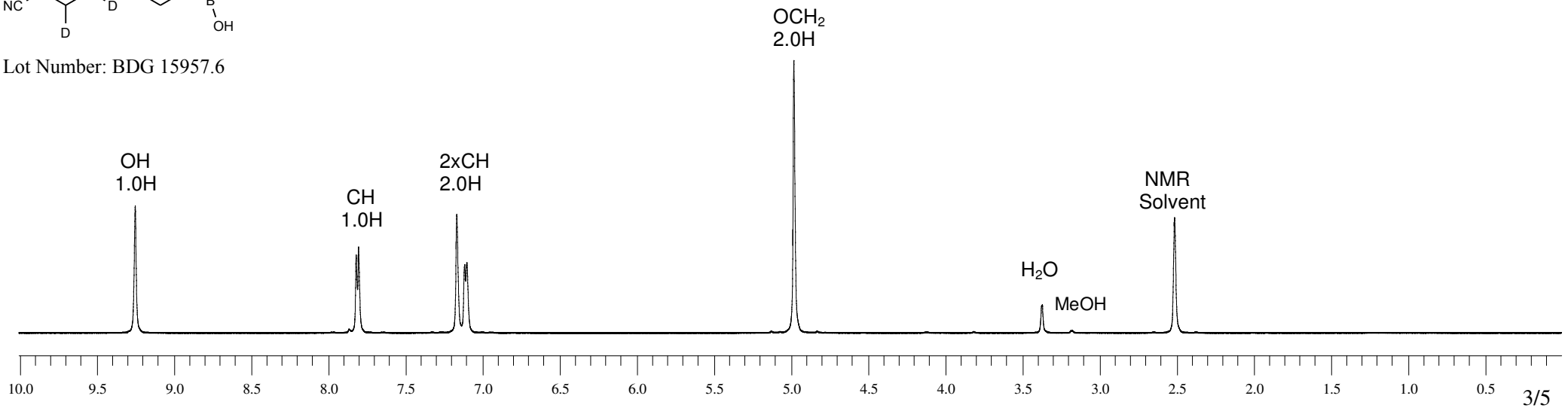
BDG SYNTHESIS

Proton NMR Spectrum of Crisaborole (top) and Crisaborole-d_4 (bottom) in DMSO-d_6



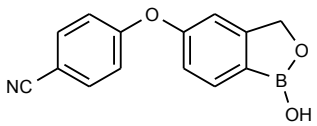


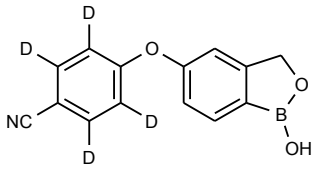
Lot Number: BDG 15957.6



BDG SYNTHESIS

Carbon-13 NMR Spectrum of Crisaborole (top) and Crisaborole-d_4 (bottom) in DMSO-d_6





Lot Number: BDG 15957.6

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Acq. Operator    : Bruce Hamilton                  Seq. Line :   8
Acq. Instrument  : Instrument 1                     Location : Vial 1
Injection Date   : 8/27/2018 3:47:43 PM                 Inj :   1
                                                  Inj Volume : 10 µl
Acq. Method      : C:\CHEM32\1\METHODS\2018\LC20024A.M
Last changed     : 8/27/2018 3:12:52 PM by Bruce Hamilton
Analysis Method  : C:\CHEM32\1\METHODS\2018\LC20024A.M
Last changed     : 8/27/2018 5:37:32 PM by Bruce Hamilton
Method Info      : BDG - Analysis of Crisaborole-d4
                   Column : Phenomenex Luna C18(2) 5 um 250 x 4.6 mm : Guard C18RP 4 x 3 mm
                   Mobile Phase A : 80:20 10 mM KH2PO4 pH=3.00 : Acetonitrile
                   Mobile Phase B : 30:70 10 mM KH2PO4 pH=3.00 : Acetonitrile
                   Gradient (A:B) : T0=100:0, T20=0:100, T24=0:100, T25=100:0, T30=100:0
                   Flow : 1 ml/min.,   Column Temperature : 30 C,    Injection : 10 ul,
                   Detection : UV at 252 nm,    Sample Solvent : 70:30 H2O : CH3CN
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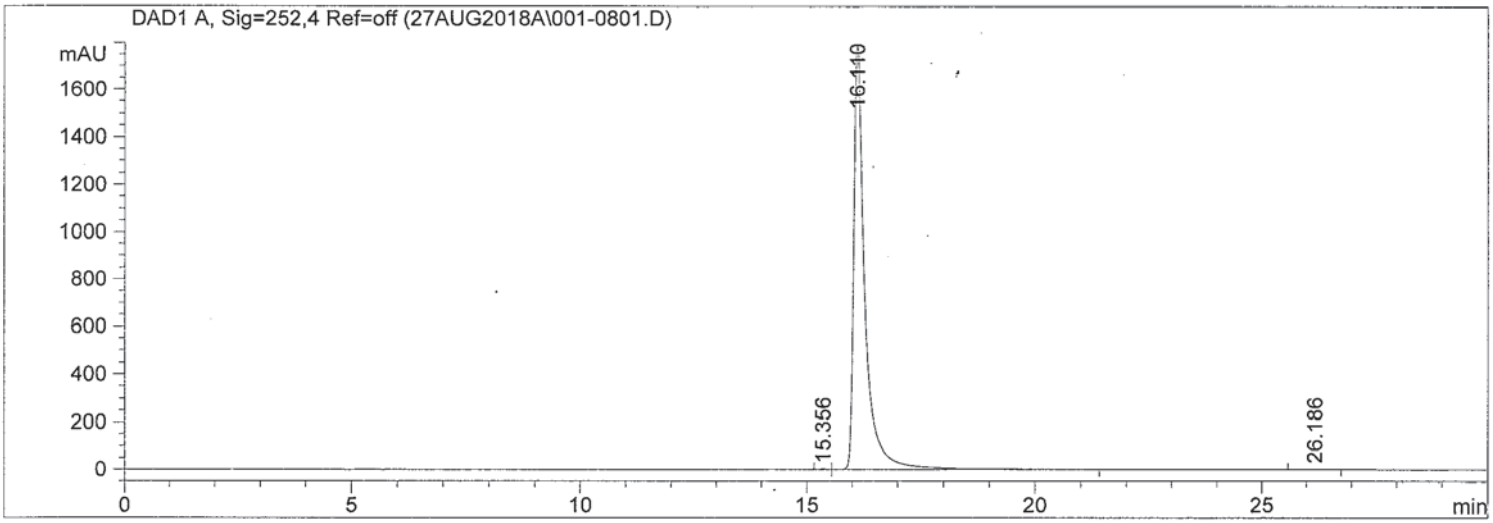


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==========================================================================
                          Area Percent Report
==========================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: DAD1 A, Sig=252,4 Ref=off

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  15.356 BV    0.1082   13.58010    1.92757   0.0434
   2  16.110 VB    0.2509 3.12134e4  1794.96008  99.8486
   3  26.186 BB    0.2367   33.74510    2.10822   0.1079

Totals :                  3.12607e4  1798.99587

==========================================================================
                          *** End of Report ***
```